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,

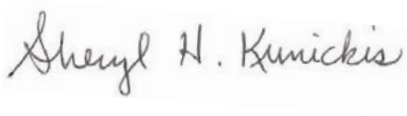
USDA appreciates the opportunity to comment on EPA's proposal to revoke chlorpyrifos tolerances, and in particular the new underlying risk assessment that was announced on November 17, 2016 ("Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment," 81 FR 81049, Docket 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,



Sheryl H. Kunickis, Ph.D.
Director

Office of Pest Management Policy
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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.

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.

EPA/OPP Meetings with Stakeholders on Chlorpyrifos
Spring – Summer 2019

May 2, 2019: Meeting with Corteva to Discuss Chlorpyrifos Status
The EPA met with representatives of the chlorpyrifos registrant, Corteva, to discuss the status of EPA's registration review, and if any additional information is needed from Corteva. The agency provided an update and Corteva discussed the uses critical to growers in terms of usage and resistance management.

May 10, 2019 and June 13, 2019: Meetings with Corteva to Discuss Chlorpyrifos Uses
The EPA met with representatives of the chlorpyrifos registrant, Corteva, to discuss uses critical to growers in terms of usage and resistance management across different regions of the U.S. As the EPA continues to work through the registration review of chlorpyrifos, this additional information may be used in refining the drinking water assessment once provided by the registrant.

June 6, 2019: Meetings with California Department of Pesticide Regulation (CDPR) and the California Almond Board
The EPA met with CDPR and the California Almond Board to discuss the review status of certain conventional pesticides at the EPA and CDPR, including chlorpyrifos. Both the EPA and CDPR provided an update.

July 10, 2019: Meeting with Corteva to Discuss Chlorpyrifos Oxon Study
The EPA met with Corteva to discuss Corteva's proposed study designed to investigate whether chlorpyrifos oxon as administered through drinking water to rats has the ability to inhibit cholinesterase activity. The EPA is always open to receipt of data that may help refine its risk assessments and committed to review a protocol for its proposed study.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

Memorandum

SUBJECT: Transmittal of Meeting Minutes and Final Report for the Federal Insecticide, Fungicide and Rodenticide Act, Scientific Advisory Panel (FIFRA SAP) Virtual Meeting held on September 15-18, 2020

TO: Edward Messina, Esq.
Acting Office Director
Office of Pesticide Programs

FROM: Tamue Gibson, MS
Designated Federal Official
Peer Review and Ethics Branch
Mission Support Division
Office of Program Support

Gibson, Tamue
Digitally signed by Gibson, Tamue
Date: 2020.12.15 12:36:33 -05'00'

THRU: Steven Knott, MS
Branch Chief
Peer Review and Ethics Branch
Mission Support Division
Office of Program Support

STEVEN KNOTT
Digitally signed by STEVEN KNOTT
Date: 2020.12.15 14:39:16 -05'00'

Jacqueline Mosby
Divison Director
Mission Support Division
Office of Program Support

JACQUELINE MOSBY
Digitally signed by JACQUELINE MOSBY
Date: 2020.12.16 08:56:36 -05'00'

Please find attached the meeting minutes and final report for the FIFRA Scientific Advisory Panel public virtual meeting held via phone and webcast on September 15-18, 2020. This report addresses a set of scientific issues being considered by the U.S. Environmental Protection Agency regarding the Office of Pesticide Programs' Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment.

Attachment

cc:
Alexandra Dunn
Tom Tyler
David Fischer
Carol Ann Siciliano
Cheryl Dunton
Anna Lowit
Dana Vogel
Monique Perron
OPP Docket

FIFRA Scientific Advisory Panel Members

Jeffrey R. Bloomquist, PhD
Robert E. Chapin, PhD (Chair)
Gaylia Jean Harry, PhD
Rebecca L. Smith, DVM, PhD
Clifford P. Weisel, PhD
Raymond S.H. Yang, PhD

FQPA Science Review Board Members

Veronica J. Berrocal, PhD
Harvey J. Clewell, PhD, DABT, FATS
Holly Davies, PhD
Marion F. Ehrich, RPh, PhD, DABT, ATS
Penelope A. Fenner-Crisp, PhD
Helena T. Hogberg, PhD
David A. Jett, PhD
Mark S. Johnson, PhD
John C. Lipscomb PhD, DABT, FATS
Kenneth Portier, PhD
Daniel M. Quinn, PhD
Pamela J. Spencer, PhD, DABT
Lisa M. Sweeney, PhD, DABT, CHMM

FIFRA Scientific Advisory Panel
Meeting Minutes and Final Report
No. 2020-02

Peer Review of the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment

September 15-18, 2020

FIFRA Scientific Advisory Panel Meeting

Held via Phone and Webcast
(Virtual Meeting)

NOTICE

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), Scientific Advisory Panel (SAP) is a Federal advisory committee operating in accordance with the Federal Advisory Committee Act (FACA) and established under the provisions of FIFRA as amended by the Food Quality Protection Act (FQPA) of 1996. The FIFRA SAP provides advice, information, and recommendations to the U.S. Environmental Protection Agency (EPA or Agency) Administrator on pesticides and pesticide-related issues regarding the impact of regulatory actions on health and the environment. The SAP serves as a primary scientific peer review mechanism of the EPA, Office of Pesticide Programs (OPP), and is structured to provide balanced expert assessment of pesticide and pesticide-related matters facing the Agency. The FQPA Science Review Board members serve the FIFRA SAP on an *ad hoc* basis to assist in reviews conducted by the FIFRA SAP. The meeting minutes and final report are provided as part of the activities of the FIFRA SAP.

The FIFRA SAP carefully considered all information provided and presented by the Agency, as well as information presented by the public. The minutes represent the views and recommendations of the FIFRA SAP and do not necessarily represent the views and policies of the Agency, nor of other agencies in the Executive Branch of the federal government. Mention of trade names or commercial products does not constitute an endorsement or recommendation for use.

The meeting minutes and final report do not create nor confer legal rights nor impose legally binding requirements on the EPA or any other party. The meeting minutes and final report of the September 15-18, 2020 FIFRA SAP meeting represent the SAP's consideration and review of scientific issues associated with "The Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity For Human Health Risk Assessment." Steven Knott, MS, FIFRA SAP Executive Secretary, reviewed the minutes and final report. Robert E. Chapin, PhD, FIFRA SAP Chair, and Tamue Gibson, MS, FIFRA SAP Designated Federal Official, certified the minutes and final report, which is publicly available on the SAP website http://www.epa.gov/sap under the heading of "Meetings" and in the public e-docket, Docket No. EPA-HQ-OPP-2020-0263, accessible through the docket portal: http://www.regulations.gov. Further information about FIFRA SAP reports and activities can be obtained from its website at http://www.epa.gov/sap. Interested persons are invited to contact Tamue L. Gibson, MS, SAP Designated Federal Official, via e-mail at gibson.tamue@epa.gov.

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No. 2020-02

Peer Review of the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment

September 15-18, 2020

FIFRA Scientific Advisory Panel Meeting

Held via Phone and Webcast
(Virtual Meeting)

Robert E. Chapin, PhD
FIFRA SAP Chair
FIFRA Scientific Advisory Panel

Robert E Chapin

Date: 14 Dec 2020

Tamue L. Gibson, MS
Designated Federal Official
Office of Program Support

Gibson, Tamue Digitally signed by Gibson, Tamue Date: 2020.12.15 11:57:46 -05'00'

Date:

Federal Insecticide, Fungicide, and Rodenticide Act
Scientific Advisory Panel Meeting
September 15-18, 2020

Peer Review of the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment

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LIST OF ACRONYMS AND ABBREVIATIONS

AC50	Activity Concentration at 50% of Maximal Activity
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase Inhibition
AED	Administered Equivalent Dose
AIC	Akaike Information Criterion
AUC	Area Under the Curve
BMD	Benchmark Dose
CCA	Comparative Cholinesterase Assays
ChE	Cholinesterase
CNS	Central Nervous System
CV	Coefficient Variation
DAT	Dopamine Transporter
DDEF	Data Derived Extrapolation Factors
DIV	Days In vitro
DMSO	Dimethyl Sulfoxide
DNT	Developmental Neurotoxicity
EFSA	European Food Safety Authority
EPA	United States Environmental Protection Agency
HCI	High Content Imaging
HEC	Human Equivalent Concentration
hNP1	Human Alpha-Defensin-1
HSUS	Humane Society of the U.S.
HTS	High-Throughput Screening
HTTK	High-Throughput Toxicokinetic
NAM	New Approach Methodology
IVIVE	In vivo-In vitro extrapolation
MEA	Microelectrode Arrays
NFA	Network Formation Assay
NOAEL	No-Observable-Adverse-Effect level
NOG	Neurite Outgrowth
OED	Oral Equivalent Dose
OP	Organophosphates
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
PBPK	Physiologically Based Pharmacokinetic
PCRM	Physicians Committee for Responsible Medicine
PD	Pharmacodynamic
PETA	People for the Ethical Treatment of Animals
PK	Pharmacokinetic
POD	Point of Departure
RBC	Red Blood Cells
RfD	Reference Dose
SAS	Statistical Analysis System

SERT	Serotonin Transporter
SD	Standard Deviation
TTC	Threshold of Toxicological Concern
UF	Uncertainty Factor

INTRODUCTION

The Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel completed its review of the set of scientific issues being considered by the Environmental Protection Agency regarding the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity For Human Health Risk Assessment. Advanced notice of the meeting was published in the Federal Register on June 17, 2020. The peer review public virtual meeting was held September 15-18, 2020. The Agency position paper, charge questions, and related documents in support of the SAP meeting are posted in the public e-docket at http://www.regulations.gov (ID: EPA-HQ-OPP-2020-0263). Robert E. Chapin, PhD, chaired the meeting. Tamue L. Gibson, MS, served as the Designated Federal Official.

In preparing these meeting minutes and final report, the Panel carefully considered all information provided and presented by the Agency presenters, as well as information presented by public commenters. The meeting minutes and final report address the information provided and presented at the meeting, especially the Panel response to the Agency charge.

The U.S. EPA presentations were provided during the FIFRA SAP meeting by the following (listed in order of presentation):

September 15-18, 2020: Summary of Meeting Agenda

Day 1 – September 15, 2020

Opening of Meeting – Tamue L. Gibson, MS, Designated Federal Official, EPA, Office of Chemical Safety and Pollution Prevention (OCSPP), Office of Science Coordination and Policy (OSCP)

Introduction and Identification of Panel Members – Robert E. Chapin, PhD, FIFRA SAP Chair

Greetings and Introduction from the Office Director and Division Director– Edward Messina, Acting Office Director, EPA, Office of Pesticide Programs (OPP); Dana Vogel, Division Director, EPA, OPP, Health Effects Division (HED)

OPP Technical Presentation –Introduction and Overview of the Regulatory Use of the New Approach Methodologies (NAMs) – Monique Perron, ScD, EPA, OPP, HED

Welcome – Alexandra Dapolito Dunn, Esq, Assistant Administrator, EPA, OCSPP

OPP Technical Presentation (Continued) –Introduction and Overview of the Regulatory Use of the New Approach Methodologies (NAMs); Developmental Neurotoxicity (DNT) Guideline and Regulatory Context for Organophosphate (OP) Case Study – Monique Perron, ScD, EPA, OPP, HED

Introduction to DNT NAM Assay Development and the US EPA Network Formation Assay – Tim Shafer, PhD, EPA, Office of Research and Development (ORD), Center for Computational Toxicology and Exposure (CCTE)

US EPA High Content Imaging (HCL) Cellular Event Assays for Assessing Chemical Effects on Neurodevelopment Processes – Joshua Harrill, PhD, EPA, ORD, CCTE

Overview of International DNT NAMs Efforts – Tim Shafer, PhD, EPA, ORD, CCTE

DNT-NAMs: Fit-For-Purpose, Results with Organophosphates and Administered Equivalent Dose Comparison to *In Vivo* Benchmark Doses for Acetylcholinesterase Inhibition – Katie Paul Friedman, PhD, EPA, ORD, CCTE

Use of *In Vitro* Acetylcholinesterase Inhibition Data to Develop Data- Derived Extrapolation Factors – Monique Perron, ScD, EPA, OPP, HED

Day 2 – September 16, 2020

Opening of Meeting – Tamue L. Gibson, MS, Designated Federal Official, EPA, OCSPP, OSCP

OP *In vitro* Inhibition Program: Introduction to Testing Program – Richard Reiss, ScD, GVP, Principal Scientist, Exponent

Experimental Procedures and Results – Janice Chambers, PhD, Professor, Mississippi State University

Statistical Analysis of Data – Kelly Higgins, PhD, Senior Scientist, Exponent

Results of Supplemental Variability Study – Richard Reiss, ScD, GVP, Principal Scientist, Exponent and Kristin Lennox, PhD, Managing Scientist, Exponent

Biological Understanding of Interspecies and Intraspecies Variability –Rudy Richardson, ScD, Professor, University of Michigan

PUBLIC COMMENTERS

Oral statements were presented by:

1) Richard Reiss, ScD, On behalf of the OP Coalition of Registrants

2) Kristie Sullivan, MS, Physicians Committee for Responsible Medicine (PCRM)

3) Anna van der Zalm, MS, People for the Ethical Treatment of Animals (PETA)

Written statements were provided by:

1) Vincent Cogliano, Deputy Director for Scientific Programs, California Office of Environmental Health Hazard Assessment and Karen Morrison, Assistant Director and Chief Science Advisor, California Department of Pesticide Regulation

2) Amy Clippinger, Vice President of Regulatory Testing, PETA; and Kristie Sullivan, Vice President for Research Policy, PCRM

3) Vicki Katrinak, Manager, Research and Testing, Animal Research Issues, Humane Society of the U.S. (HSUS); and Gillian Lyons, Senior Regulatory Specialist, Humane Society Legislative Fund

4) Rudy J. Richardson, Exponent on behalf of AMVAC et al.

5) Anne Loccisano and Rick Reiss, Exponent on behalf of Dow Agrosciences LLC

6) Rick Reiss and Benjamin Davis, Exponent on behalf of the Coalition of OP Registrants

7) Kristin Lennox and Rick Reiss, Exponent on behalf of FMC Corporation, AMVAC Chemical Company and Gowan Company

8) Rick Reiss, Exponent on behalf of Coalition of OP Registrants

EXECUTIVE SUMMARY

New Approach Methodologies (NAMs) for Developmental Neurotoxicity (DNT)

Developmental neurotoxicity refers to "any adverse effects on the normal development of the nervous system structure or function". The current EPA DNT guideline study requires an assessment of motor and sensory function, learning and memory, and neuropathology following maternal exposure. The EPA has shifted its testing focus from the developmental neurotoxicity guideline study to more targeted testing due to several challenges associated with the study and its limited impact on human health risk assessments for pesticides. The Agency stated a long-term goal of replacing the DNT guideline due to shortcomings and challenges that have been identified with guideline study data obtained for pesticides. As suggested by the Agency, and inherent in all types of experiments, the quality of these data sets depends on multiple factors that require appropriate expertise and oversight in how the experiments are conducted to control for factors that can increase variance and thus, hinder data interpretation. This has resulted in data submitted to the Agency with a high level of variability. The Panel was not provided information related to the quality and variance of the *in vivo* DNT guideline data sets received by the Agency and only a few of the Panel members had any level of knowledge of the specifics of these assays and the issues of concern. However, the Panel found it clear that the Agency has had issues with DNT guideline study data submitted in meeting their expectations for interpretation of risk.

The Agency considers new approach methodologies (NAMs) that represent non-animal technology, methodology, approach, or combination thereof will provide an opportunity to overcome some of these challenges by evaluating underlying critical processes of neurodevelopment and incorporating human relevant information. These NAMs are considered by the Agency as "something more efficient, less animal intensive, and importantly more human relevant" and "easier to interpret." The Agency made a decision to follow a phenotypic approach for establishing NAMs for developmental neurotoxicity, not unlike the approach taken of apical endpoints for the *in vivo* assessments. The suite of NAMs applied in this manner investigate a number of cellular endpoints likely to be involved in neurotoxic effects, developmental and across the lifespan. In the assay development, important neurodevelopmental processes were modelled with cell-based phenotypic endpoints. Evaluation of specific NAMs for neurotoxicity have been undertaken to determine if they can be used to supplement or to replace existing toxicity tests. The Panel was asked to provide guidance on establishing confidence in the use of the data obtained from the specific NAMs presented. Feedback was solicited with regards to strengths and limitations, adequate reflection of the relevant neurodevelopmental biology, and sufficient development and validation such that data may be incorporated into the assessment of a chemical's effects on neurodevelopment.

The Panel understood the policy requirements of the EPA to move beyond animal testing. The Panel noted that the isolated culture systems lack some features that are known to be critical in the development of the nervous system. The Panel identified numerous limitations and points for consideration that applied to the first three charge questions. It must be acknowledged that given the complex nature of development and the gaps in our current knowledge on these processes, *in vitro* assays may not be representative of many processes and mechanisms that could cause developmental neurotoxic events. These are isolated cell cultures that do not include

inter-organ/tissue communication/effects, peripheral/central influences, and, while powerful in examining specific mechanisms, they may not reflect *in vivo* condition. Statistical differences between exposures in culture may not be representative of actual *in vivo* effects. In the Agency's presentation it was stated that "Decision makers need to understand what endpoint we're measuring, how it is measured, and how that relates to changes and neurodevelopment *in vivo*." In the EPA Issue Paper, it was expected that "Incorporating a battery of NAMs to the evaluation of DNT would also aid in the data interpretation by providing multiple lines of evidence that may help elucidate the biological processes underpinning the apical endpoints affected in the guideline studies." The Panel noted that it was not clear how the NAMs, as stated, will provide such information. Specificity of the target site in the nervous system and much of the circuitry involved in each of the *in vivo* DNT endpoints was not represented in the NAM.

Neurotoxicity does not only occur with direct exposure of the brain to chemicals, it also occurs due to secondary effects from changes in the peripheral environment. For developmental neurotoxicity, these effects can be due to changes that occur in the peri-partum environment (e.g., maternal) as well as due to compromised function of the peripheral organ systems. Specific concerns include:

a. The absence of hormonal factors (sex hormones, thyroid, stress hormones)
b. The influence of neurotransmitter signaling
c. The influence of chemical-induced systemic changes (e.g., inflammation, oxygen levels and distribution)
d. The influence of maternal factors (maternal infection, hormonal, organ system dysfunction, placenta integrity)

In addition, the *in vitro* assays:

a. Will be limited in their ability to detect adaptive or compensatory processes
b. Do not account for critical cell-cell interactions required during neurodevelopment
c. Have difficulty distinguishing between neuroactive and neurotoxic compounds
d. Do not reflect human genetic diversity when using human cell lines from one human

As presented, the NAMs do not include all the different cell types critical during neurodevelopment.

It was not clear to the Panel that a median response in the *in vitro* assays could be directly related to a meaningful point of departure useful in predicting a disease state in humans.

Generally, the Panel thought that these assays constituted an excellent screen, but wondered about their utility in their proposed use to ultimately define a safe level of exposure.

As the assays are performed it was not evident to most Panel members that they would contribute to any understanding of mechanisms.

The Panel considered the efficacy of the *in vivo-in vitro* extrapolation (IVIVE) approach, and the various assumptions involved in its use, for projecting from NAM-derived administered equivalent dose (AED) values to OP doses that inhibit acetylcholinesterase (AChE) in humans and rats. The Panel noted that the development of the NAM technology and the consequent high-throughput toxicokinetic (HTTK) model for IVIVE represented considerable advances

toward the goal of eventually eliminating evaluation of environmental toxicants, specifically organophosphorus (OP) inhibitors of AChE, in laboratory animals. However, the Panel raised a number of concerns. Prominent among the concerns was the adequacy of the HTTK model to account for predictive OP dosing, since extrahepatic metabolic mechanisms are not taken into account. Another concern was the use of data in one species for IVIVE in another. Various recommendations for addressing these and other concerns are detailed in the following discussion.

The analysis does not follow EPA guidance on Data Derived Extrapolation Factors, and the justification for the type (tissue, lifestage, ethnicity) and number of samples analyzed does not support an acceptable level of confidence regarding the breadth of the analysis. These and other conditions complicate the acceptance of presently proposed values for inter- and intraspecies toxicodynamic variability. Data collected to date may be reinterpreted to satisfy some, but not all the issues identified in this review.

The Panel noted that the approach to model-fitting represents current good statistical practice and seems well thought out. Use of an Akaike Information Criterion (AIC) is a typical measure used to choose among different models. Graphical diagnostics are used extensively to supplement AIC in final model selection. The Statistical Analysis System (SAS) code aligns with the description provided in the EPA Issue Paper but includes few comment statements other than indicating which scenario was being addressed and which model was being fitted.

Justifications were not provided as to why default model fitting options were changed for the model being fitted. The logic and/or analysis approach was not presented or documented but has to be inferred by looking at which fit options have been changed from the defaults.

The Exponent analysts expressed proper concern and understanding of the importance of the model fit warnings output by SAS©. The Panel observed that The approach used by the Agency's statistical contractor, ICF to address these model fit concerns, namely the incorporation of parameter scaling, setting the maximum number of search iterations higher, and the use of "ridge" estimation, was reasonable and represents good statistical practice. Most of the model issues were likely tied to a lack of representativeness in available samples and too few sample data points for the model being attempted. The Panel suggested a few additional analysis to address model fit warning issues in the future. For some scenarios the outlier issue reflects the fact that the underlying data display characteristics that are in conflict with the assumptions of the model.

Multiple Panel members agreed that the stratified analyses used to derive values for the bimolecular rate constant ratios employed sample sizes too small to guarantee reliable results. In particular, several Panel members noted the limited availability or absence of samples representing certain ethnic and racial groups, as well as an over-representation of some demographic groups over others, specifically juveniles and infant, compared to the US general population. Several Panel members recognized the supplemental efforts undertaken by ICF to address issues related to model fit. However, Panel members noted that due to the small sample sizes, several issues still persisted, including convergence problems, standard errors estimated to be equal to zero, and extreme outliers.

Several Panel members recommended that efforts be undertaken to increase the sample size, leveraging on planned research efforts at Mississippi State University under the sponsorship of a consortium of companies. A Panel member noted a large variability in the bimolecular rate constant values relative to Naled (a proinsecticide that is known to break down in aqueous media to dichlorvos, a high volatility compound), and indicated possible reasons for the extreme variability in data relative to Naled.

Some members of the Panel believed that from a conceptual point of view, an analysis that uses replicate data to characterize human variability in response to organophosphate exposure was the correct approach. The same Panel members also considered a linear mixed model approach and the IntraClass Correlation the right metric to quantify the extent of human variability in response to organophosphate exposure compared to the total variability (human + experimental variability).

All Panel members recognized that the current replicate analyses use a very small sample size, resulting in tests that are underpowered. Due to the very small sample size, a Panel member recommended that coverage ratios for the bimolecular rate constants k_i be calculated using a different approach than that used currently, which relies on approximations due to large sample size.

The Panel was supportive of the idea of additional replicated data analysis to characterize the sources of variability in the human response to exposure to different organophosphates. The Panel recommended that a larger sample size with samples that are more representative of the US general population be used in these additional replicated data analyses. Some Panel members recommended a better accounting for all sources of uncertainty, such as handling the differences between chemical properties of organophosphates, the nature of the data (not actual observed data, but derived quantities, point estimates), and the uncertainty associated with extrapolation of cellular responses to responses of whole biological systems.

PANEL DISCUSSION AND RECOMMENDATIONS – New Approach Methodologies for Developmental Neurotoxicity

Charge Question 1. – ***New Approach Methodologies for Developmental Neurotoxicity***

Question 1. *For charge questions 1-3, the overall focus is on the ability of the developmental neurotoxicity (DNT)-new approach methodologies (NAMs) to evaluate important biological processes related to neurodevelopment. EPA is soliciting feedback on whether the NAMs adequately reflect the biology such that data may be incorporated into the assessment of a chemical's effects on neurodevelopment.*

Using primary rat cortical neurons grown on microelectrode arrays (or MEAs), the EPA's Office of Research and Development has developed a network formation assay (NFA) to assess the potential impact of chemical exposure on neural network formation and function as described in Sections 2.3.1 - 2.3.4 of the Agency's Issue Paper. *Please comment on the strengths and limitations of using this assay to evaluate the biology underlying network formation as a component of neurodevelopment that may be susceptible to modulation by chemical exposure.*

The neuronal system for network formation assay (NFA) presented by the EPA was rodent cortical neurons. These cells form densely organized cellular networks and become electrically active after a few weeks in culture. Typically, differentiated neurons are comprised of a cell body from which neurites (dendritic tree) and a single long cylindrical axon emerge. These structures adhere to MEAs substrates by electrostatic or chemical interactions between adhesion molecules that protrude from the lipid membrane of the neurons and molecules deposited on the MEA platforms. An ionic solution fills the cleft between the cell membrane and the MEA substrate. In Section 2.3.1. of the EPA Issue Paper, the assay defines relevant signaling endpoints as parameters that indicate general and bursting activity as well as a calculated network spikes. The MEA methodology has been around for a number of years and, with technological advancements as well as data capture and analysis, the commercial systems offer an attractive method to try to examine neuronal connectivity *in vitro* to study cell-cell communication.

Strengths:

Rapid, high-throughput screening (HTS) format; functional endpoint of neuronal activity; ability for repeated measures over time; ability to compare acute responses versus disruption of cell development with exposure.

Several Panel members noted strengths of the NFA including assessment of functional endpoints that could serve as descriptive apical endpoints, the ability to examine different stages of exposure, and the ability to record repeated measures over time.

The NFA allows for a level of limited high-throughput, making it suitable for screening compounds. One Panel member noted that the MEA NFA often finds effects at or below the lower quartile of the Toxcast/Tox21 activity concentration at 50% of maximal activity (AC50) values (US EPA 2020b, pages 8-9).

The Panel noted additional strengths of the MEA NFA in that the anatomical features of the cells can be further examined by incorporating additional imaging and/or immunohistochemical methods. Comparison of effects that are dependent upon prolonged exposure, DIV age dependent exposure, acute chemical presence, could provide information on developmental versus neurotoxic/active effects. The ability to examine cell viability, growth, maturation, in addition to spontaneous activity can provide information for data interpretation. The NFA has the ability to expand to include targeted neuron to neuron signaling and allows for supportive information on alterations in neuronal network signaling.

The NFA assay as described was amenable to further examination to integrate with other endpoint assessments such as molecular profiling or biochemical endpoints with pharmacological modulations to identify the "underlying biological effects". With optimization, the MEA NFA paradigm can be used to examine different neuronal populations.
The application of rodent cortical cells has the benefit of a deep literature base for the *in vitro* establishment and use of these cells in neurobiology. Additionally, they represented a primary culture containing neurons and astrocytes which avoids constraints associated with cell lines or with manipulations required to differentiate cells into neurons. The use of rodent cells allows for the generation of cells from males or females and for the design of future studies to evaluate and predict validity of effects observed *in vivo*. No data was presented to compare sensitivity across species to support usage of any specific cell source. The inclusion of astrocytes was a strength. However, the assay design does not allow for distinguishing if effects on network formation are related to effects on neurons or astrocytes.

In vivo, circuitry development and orientation relies heavily on the lamination of brain structures (e.g., cortex, hippocampus, cerebellum) and cell-cell signaling. In contrast, *in vitro* neural network formation depends on cell specific recognition cues rather than orderly lamination to promote specificity of synaptic connectivity (Williams et al., 2011). The random nature of the network may not be a critical factor for screening; however, the Panel recommended caution for translating to brain development.

Limitations:

Difficulty detecting adaptive changes; lack of inclusion of neuroendocrine/neurotransmitter interactions; difficulty distinguishing neuroactive from neurotoxic compounds; high variability. Several Panel members noted the MEA NFA, such as the high content imaging (HCI) assays, lacked any contribution of hormone levels and/or changes in neurotransmitters. This gap can impact the ability of the assay to detect adaptive or compensatory processes. Moreover, the assay will have difficulty distinguishing between neuroactive and neurotoxic compounds (i.e. lead to more false positives).

Assay variability was raised by several Panel members who considered the coefficient variation (CV) of the assay parameters as too high (often >15%). Another Panel member thought it reflected appropriate variation based on the biological complexity of the measurement. The Panel noted that more targeted data will be required to determine if this level of variability is inherent in the biological endpoint being measured.

The Panel considered that, as a standalone test, the MEA NFA will not detect all potential DNT compounds as the target (e.g. early windows of development or certain cell types (e.g. dopaminergic neurons and oligodendrocytes)) might not be present. However, the Panel generally agreed that the assay, if used in conjunction with a battery of assays (i.e. DNT NAMs), is an appropriate screening tool for neuronal function.

Other Limitations:

One Panel member commented that many compounds will show a neuro-excitation effect at low concentrations and fast nerve block at high concentrations. Due to this, the Panel considered the question of which measured effect was most appropriate for evaluating assay performance. The Panel considered the need for additional known positive controls with domoic acid. It was noted by the same Panel member that, by including more specific neuroactive compounds, additional positive effects on general activity, bursting activity etc. would have addressed a current deficiency (US EPA 2020a, page 30).

Several Panel members cautioned that an *in vitro* test system does not sufficiently represent the *in vivo* environment nor do changes *in vitro* translate to effects on development. The NFA, measured signaling sites and spontaneous activity however, translating this to representing mature synaptic signaling across defined neuronal networks was recommended to be done with a high level of caution. A critical process of network formation is related to the stages where neurons undergo a phase of overconnectivity, followed by synaptic pruning and thus, a refinement of network formation and activity. The exposure paradigm of the NFA does not take this developmental process into consideration.

One Panel member commented that there was a need for empirical data that showed *in vitro* concentrations represented relevant *in vivo* nervous system concentrations to cause developmental neurotoxic effects. In some cases, it has been compared with blood and brain acetylcholinesterase (AChE) activities, but not developmental toxicity. *In vitro* to *in vivo* extrapolation (IVIVE) was considered as a tool to help inform if an *in vitro* change was sufficiently representative of a plasma concentration that could lead to an adverse outcome.

Panel members offered the following comments related to concerns with underlying assumptions or enhancing the experimental paradigm of the assay:

- Trying to control or standardize the cultures for cell density with prolonged exposure may be difficult if processes in the earlier days *in vitro* (DIV) were affected. This could affect data interpretation in that the resulting differences in network signaling could represent a difference in cell maturation or a difference in cell signaling ability. While standardization approaches were mentioned by the Agency, unless this is a one-to-one relationship, the standardization techniques might not reflect the biological differences.
- Discriminating between effects on cell signaling occurring as a result of exposure over DIV, or effects occurring within the earlier DIV, versus effects occurring due to the presence of the chemical was not possible given the experimental design presented. However, the assay exposure paradigm could be modified. For example, excluding the early time point, cells at each of the DIV could be examined for the “acute” effect of the chemical to determine if any differences attributed to network signaling are due to early DIV exposure or to the presence of the chemical at the time of assay.

- Synchronized activity of rodent cortical neurons initiates at approximately embryonic day 16, increasing in frequency, then subsiding by first week of life (Corlew et al., 2004). It is thought that the acquisition of synchronous firing is a key property in the development of cortical neural networks. Further inclusion of synchronous firing might allow for examination of the pattern of network development over DIV.
- The assay paradigm makes the assumption that DIV of newly obtained neurons from the postpartum rodent brain recapitulates the brain development process.
- In analysis of the data, the interdependency of many of these endpoints and the complexity of the system may require a different framework than what has been done in the ToxCast arena. Since 2018, there have been a number of papers published dealing with the use of a deep learning framework for classifying data from MEA. Many of these approaches are designed to address the biology underlying the MEA data and to consider how to examine the data in a manner that will decrease variability (Buccino et al., 2017; 2018a,b).

Beneficial asymptomatic seizures are important in brain development, especially during pruning. Determining how the MEA NFA can be designed to detect chemicals with seizurogenic properties or those that may inhibit seizure activity will be of importance in data interpretation. Several Panel members commented on the need to ensure the quality and reproducibility of the data between laboratories through well-developed standard operating procedures (SOPs) for designing and conducting the studies. In the case of the EPA's Office of Research and Development (ORD), they are fortunate to have the level of expertise to carry out robust standard operation procedures (SOP) formulation.

Recommendations:

The Panel recommended a number of avenues for developing the use of the MEA NFA to provide information into the realm of "developmental neurobiology/toxicology" that would be of benefit to the Agency and use of the data for risk assessment. These include:
1) Opportunities to expand and develop the MEA NFA further, with a focused effort, given the potential to be able to integrate this assay with other endpoint assessments (e.g. molecular profiling to try to identify "underlying biological effects").
2) Deeper, targeted examinations of the associated underlying mechanism using either a more complex approach or proposed deep learning analysis of the data.
3) Modifications of the assay to include additional aspects of response rather than relying solely on spontaneous activity.
4) Electrochemical impedance spectroscopy to study cell adhesion and growth,
5) Pharmacological methods to modify the chemical response
6) Evaluating the specific chemicals that inhibit AchE (ranged from 0.03 micromolar to 10 micromolar), concentration should be considered that are based on AchE inhibition including doses below those that inhibit AchE doses and doses above steady state inhibition.
7) Inclusion of an explanatory figure describing general activity/burst rate (US EPA 2020a, Table 1).

The Panel concluded that the MEA NFA has the potential to go beyond the realm of "screening for chemical prioritization" to developing a more "fit for purpose" approach to identify "underlying biology" of neurodevelopmental processes as relevant to the specific question at

hand. Such an integrated, composite approach could be used to evaluate not only the cell signaling readout for other chemicals but also classification of critical biological events.

Charge Question 2. – ***New Approach Methodologies for Developmental Neurotoxicity***

Question 2. The EPA's Office of Research and Development has used high content imaging (or HCI) with a variety of rat- and human-derived *in vitro* models to investigate the potential impact of chemical exposure on cell proliferation, apoptosis, neurite outgrowth, and synaptogenesis as described in Sections 2.3.1 - 2.3.4 of the Agency's Issue Paper. *Please comment on the strength and limitations of using the HCI assays to evaluate the biological processes underlying proliferation, apoptosis, neurite outgrowth and synaptogenesis as components of neurodevelopment that may be susceptible to modulation by chemical exposure.*

The HCI of neuronal progenitor cell lines represented an assay utilizing human and rat lines to investigate different morphological stages and processes associated with development including cell proliferation, cell death/viability, differentiation, and process outgrowth that reflect aspects of brain development, and phenotypically may be representative of developmental neurotoxicity. The assay relies on new technology for video imaging and quantitation of distinct morphological features of cultured cells.

Strengths:

Covers several endpoints, high-throughput, automated, reproducible. The strengths of this assay are that the cell morphology aspect compliments the cell function aspects of the microelectrode array assays. It was also a method used in documenting ontogeny studies at the cellular level related to DNT from early (proliferation) to late (synaptogenesis). The HCI assays span early and late (embryonic and fetal) neurodevelopmental processes. It is a relatively high-throughput assay where several chemicals can be tested in parallel. The inclusion of human and rodent cells can be useful to identify species differences. The Panel generally agreed that no single *in vitro* screening assay can recapitulate the critical processes of neurodevelopment or affirmatively identify all chemicals that may produce DNT.

The HCI endpoints offer good reproducibility and a more statistically robust evaluation of neurodevelopment than the MEA method, particularly evident in the neurite outgrowth assay in both the rat cortical and hN2 cell lines. One might expect that the two assays would have similar responses to the vehicle dimethyl sulfoxide (DMSO), but that was not the case. There were smaller CV values calculated for the HCI parameters, compared to the MEA with the vehicle DMSO. Many (two thirds) of the HCI CV values were <10%, and only one third were >10%, and no CV values for HCI parameters were >20% (US EPA 2020a, Table 5, pages 26-27). The variability for 21 HCI CV values (mean + standard deviation (SD) = 8.74 ± 4.5) was significantly less (t-test, $p = 0.0002$) than the MEA CV values for 19 electrical parameters (CV mean + SD = 16.54 ± 7.3).

The Panel agreed that one must consider that observed differences can also be due to the cell culture differences such as cell composition, window of development, rate of development, and

media composition (e.g., binding vs. free chemicals might differ). One Panel member commented that the comparison of heatmap clustering (US EPA 2020a, Table 11) appeared to be a useful way to ascertain the weight of evidence (or probability) of a substance to cause developmental neurotoxicity. The suite of endpoints in the HCI assays may be useful as toxicity screening tools, but issues remain regarding their use in protection of developmental neurotoxic effects in humans.

Limitations:

Bias in HCI measurements; discrete assays that do not include other inter-organ interactions (e.g. neuroendocrine); absence of functional endpoint; uncertainty regarding use of AC50 concentrations; limited utility for predicting DNT mechanisms, unclear for broad utility across compounds. Several Panel members were uncertain about the utility of AC50 concentrations and questioned whether they were predictive or translate to DNT effects that occur with concentrations in human plasma associated with an adverse outcome. One Panel member commented that, while instrumentation data capture and analysis software can provide quantitative measures, human evaluation and potential bias is still possible and there are required quality control efforts to confirm that the automated data collection is capturing the specific cell morphology of concern. These are isolated systems where biological changes between systems are not accounted for (e.g., neuroendocrine effects), and the ability to extrapolate findings to in vivo neurodevelopment was a concern for several Panel members.

Many of the HCI endpoints captured phenotypic changes that may occur with multiple underlying modes of action that are likely to affect neurodevelopment. However, they do not provide information on specific mechanisms that may cause neurodevelopmental effects. Some endpoints (or modes of action) that could plausibly cause neurodevelopmental effects are absent (neurotransmitter-specific biomarkers of effect).

Generally, the Panel thought that these assays constitute an appropriate screening tool, but questioned their utility in their proposed use to ultimately define a safe level of exposure.

Other Limitations:

Several Panel members questioned the time of exposure and whether 24-48 hours (5 days for synaptogenesis) of exposure is enough to mimic developmental neurotoxicity *in vivo* beyond acute poisoning. While a window of exposure may exist for damage, the outcome is often associated with either developmental time or long-term exposure.

Another Panel member commented that the synapse formation assay only includes the presynaptic marker synapsin I and recommended that additional immunological markers be employed to determine if a synapse is formed, preferably localization with a postsynaptic marker such as postsynaptic density protein (PSD) 95.

One Panel member mentioned that when the assay-positive control chemicals were selected (US EPA 2020a, Figure 4) it would have been beneficial to show all chemicals over the assays, especially since some of them are evaluating the same endpoint (e.g. neurite outgrowth). This would benefit the understanding of differences and similarities in the various assays and how

they could complement each other or how they provided conflicting data. This approach would also be of value to evaluate the 120 chemicals in the European Food Safety Authority (EFSA) study.

The EPA Issue Paper, page 16, states that "chemicals might contribute to e.g. autism spectrum disorder, attention deficit hyperactivity disorder, though the specific neurodevelopmental mechanisms for these DNT outcomes is the subject of ongoing research efforts." It was not evident to most Panel members that HCI assays would contribute to any understanding of mechanisms of these disorders, especially as many of these outcomes are likely due to gene-environmental interactions. One Panel member commented that sex differences would not be addressed with the assay as described.

Several Panel members commented about the possible biases in HCI interpretation. The ability to automatically perform and analyze large numbers of complex endpoints and to replace human bias in image interpretation by numerical representation of cellular behavior in human and rat cell lines will be challenging. This was evident in Table 6 of the EPA Issue Paper where 2/3 of the HCI endpoints have CVs below 10%. This contrasts with the MEA NFA where nearly 70% of the endpoint CVs are above 10%. Overall robust positive controls for all the activity types measured apart from activity for human alpha-defensin-1 (hNP1) proliferation which produced effects, but of a low magnitude (US EPA 2020a, Figure 4, Table 9). It was recommended by one Panel member that assessing multiple cellular markers in a single assay may be optimal.

Several Panel members noted the lack of inter-organ effects. That they lack endocrine signaling/communication that are known to influence neurodevelopmental processes could lead to false negatives for some classes of chemicals. The assays do not eliminate animal use as some rely on animal derived cell lines (e.g. neurite outgrowth (NOG) rat cortical), though it was recognized that overall animal use will likely be decreased. Both NOG rat cortical and hN2 cell lines appear to be equally sensitive in detecting neurite outgrowth (US EPA 2020a, Table 9) although the positive control, lithium chloride, used for hN2 cell line appear to have some cytotoxicity at the effective concentration. One Panel member questioned the need for both rat cortical NOG assay relative to the hN2 cell line assay and if they showed significant species specific differences to warrant use of both. A direct comparison between the rodent and human cell lines would be a contribution to any future assay design or selection.

One Panel member noted the absence of neurotransmitter-specific biomarkers analyzed by HCI and raised the issue that this absence might cause the HCI analysis to miss this specific type of toxic effect. Such neurochemical markers could include tyrosine hydroxylase, dopamine transporter (DAT), serotonin transporter (SERT). Development and/or synaptogenesis could be skewed by a compound in favor of or against a particular transmitter type without changing overall synaptic density. The HCI assay suffered from a lack of endocrine input on development. The Panel recommended that, by using what is known about cortical neuronal development, there may be specific patterns of ion channel, receptors, or other proteins that could be leveraged as additional key or sentinel measurements of chemical insult, in addition to the general markers of synaptogenesis already proposed.

One Panel member raised the question of whether the HCI assay could be expanded to capture information on axonal and dendritic growth separately given that differential effects have been reported with chlorpyrifos (Howard et al., 2005).

Several Panel members raised questions about the utility of using postnatal cells in an assay that assesses developmental neurotoxicity where effects could occur prenatally however, another Panel member noted that cross species timing for brain development allows for a closer match across rodent and human development for cell harvest. Another Panel member recommended a requirement that the development timing of collection from rodents was determined to be optimal for predictions of *in vivo* neurodevelopmental effects and possible translation to humans. One Panel member raised concerns with making the assumption that days *in vitro* represented the developmental progression *in vivo*.

Several Panel members questioned the relevance of using a median concentration in a statistical test between treatments as the point of departure to be used in an IVIVE extrapolation effort. Since many of the positive controls can be used therapeutically, concentrations in an assay that could result in a disease state (i.e., developmental neurotoxicity) has not been determined. More justification is needed to show what magnitude of *in vitro* response in these assays translates to *in vivo* disorder. Some of the changes can be used therapeutically and may have little relevance in causing DNT at those levels and as such violates the first assumption. However, it was remarked that some of these endpoints could be refined if compared with *in vivo* responses of known effect level.

Recommendations:

The Panel recommended that the Agency consider the following:

1) Linking of morphological endpoints *in vivo* with endpoints of effect at concentrations used in the *in vitro* assays.

2) Determine the concordance of HCI studies between human neural progenitor cells and primary rat cortical neurons to obtain the value of using one versus the other cell source.

3) Inclusion of a vehicle control in every assay and consider the inclusion of a different vehicle substance rather than dimethyl sulfoxide

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Charge Question 3. – ***New Approach Methodologies for Developmental Neurotoxicity***

Question 3. As discussed in Section 2.1 of the Agency's Issue Paper, EPA has shifted its testing focus from the developmental neurotoxicity guideline study to more targeted testing due to several challenges associated with the study and its limited impact on human health risk assessments for pesticides. New approach methodologies (or NAMs) provide an opportunity to overcome some of these challenges by evaluating underlying critical processes of neurodevelopment and incorporating human relevant information. NAMs covering critical processes in neurodevelopment developed by EPA's Office of Research and Development and

researchers funded by the European Food Safety Authority are presented in Table 3 and Figure 2 of the Agency's Issue Paper (Section 2.3.2). Based on this information and considering the goal of developing a NAM testing strategy or an integrated approach to testing and assessment (or IATA) within the next year for evaluating developmental neurotoxicity to inform chemical risk assessments, *please comment on whether this NAM battery reasonably evaluates the biology underlying the critical processes related to neurodevelopment that may be susceptible to modulation by chemical exposure.*

The Panel complimented the EPA for advancing the development and critical evaluation of NAMs for DNT and for consideration in the Agency's scientific and regulatory processes. The Panel appreciated EPA's efforts to present information on the status of assays being developed in international efforts. A consideration and appreciation that one assay system will not serve to reflect the various aspects of neurodevelopment and impacts of chemical exposure was reflected in the battery of assays presented. The battery represents the EPA assays and assays developed in two European laboratories under funding by the European Food Safety Authority. Other contributions by the Danish EPA were mentioned but not presented in detail. The battery of assays was presented in Section 2.3.2, Figure 2 and Table 3 in the EPA Issue Paper. The assays presented represented three from Dr. Leist's laboratory (Konstanz University, Konstanz Germany) including a neural crest migration assay in which migration was identified by cells moving into an open plate region upon removal of a barrier. The second utilized a human H9 cell line manipulated for differentiation into dorsal root ganglion precursor cells that are then examined for alterations in neurite extension. The third assay was an immortalized human dopaminergic neuronal cell model in which neurite outgrowth was measured. Dr. Fritsche's laboratory (Leibniz Institute for Environmental Medical Research, Dusseldorf, Germany) focused on obtaining multiple endpoint assessments using rather complex neurosphere assays derived from primary human neuroprogenitor cells of fetal origin. This system allowed for evaluation of cell proliferation followed by neuronal and glial (radial and oligodendroglia) differentiation and migration of neurons preceded by radial glia similar to what can be observed *in vivo*. Using various immunological markers, the morphology of cells and various quantitative measures of cell density and migration areas can be determined.

The Agency briefly mentioned that efforts were underway in 5 different laboratories examining the utility of developmental assays in zebrafish. These studies were still ongoing, and data was not available for the Panel to provide an assessment. However, the consideration of the zebrafish model to determine if it can be demonstrated to be specific for effects on nervous system development was supported by the Panel. However, while the zebrafish may offer a method to include various systemic factors, there remain limitations in the translation of hormonal, metabolism, and simplistic behaviors.

Strengths:

Overall, the Panel agreed that the focused battery of assays was an excellent attempt to reflect, if not directly model, critical morphological processes identified as being involved in nervous system development. The individual components of the battery represented assays that could be selected as a fit for purpose and would allow additional endpoint evaluation to allow the Agency to gain a better understanding of the biological processes being recruited. The assays were currently being conducted in laboratories with the level of expertise and instrumentation

required. In addition, there was some level of redundancy of the processes measured that may allow for replication of effects. The International effort to standardize and validate the methods will be a benefit for consideration of use in regulatory decisions.

Limitations:

The Panel pointed out that several important processes and cell types were missing in the battery and that it underestimated the complexity of nervous system development. Nervous system development occurs in a very interactive manner with multiple cell types driving the temporal and spatial progression that leads to a correct formation of the neural network. These interactive processes are difficult to capture in cell models. The assay systems developed in the Fritsche laboratory offer the greatest possibility and the MEA system proposed by the Shafer laboratory offers some level of functional as well as structural assessment. The battery provides primarily structural assessments and overall lacks functional and mechanistic assessments. The phenotypic changes likely reflect functional effects occurring in the cell.

The Panel identified a significant limitation in assays covering glial cells (astrocytes, oligodendrocytes, and microglia). This was considered a major limitation as these cells comprise approximately 50% of the neural cell population and play crucial roles during development. Thus, the NAMs proposed were focused on neurons and exclude the critical functions of various glial populations and the neurovasculature unit in nervous system development. While it is critical that functional neuronal networks are formed, the ontogeny of microglia and astrocytes and their essential contributions to this process was not fully considered in the NAMs presented. The Panel noted the limited representation of the various neuronal populations (neurotransmitter type, and brain regional) and the absence of information on processes that are known to be critical for brain development such as ontogeny of neurotransmitter function (levels, receptor expressions, activation, or neurotransmitter ratio). Some Panel members noted the limitation of the assays to cover differentiation to specific neuronal types, e.g. dopaminergic, cholinergic, and serotonergic neurons and the various nervous systems (central, peripheral, autonomic). Multiple Panel members noted that neurotransmitters are not only important for nervous system function but for several developmental processes cited as critical in the design of current assays such as migration, synapse formation and neurite outgrowth. The Agency's presentation mentioned the possibility of chemicals contributing to autism spectrum disorder or attention deficit hyperactivity disorder for which published research suggested an imbalance between excitatory and inhibitory neurotransmitter signals requiring consideration of a more complex cellular interaction. Thus, for a developmental human disease with possible association with chemical exposure, the assays proposed lack a critical component for assessment.

One Panel member pointed out that the natural *in vivo* progression of neurons sending out processes was not random but rather a targeted migration to a final "correct" location to form a synapse. This migration was driven by chemotaxic and chemoattractant signals. The migration assays included in the battery do not include a directionality or signaling component but rather examine random cell movement out of a dense core for the assays in the Leist laboratory, or process outgrowth in the EPA assays or the neurosphere assay. Based upon data available in the literature, methods to evaluate response to migratory directional signals are available that could be included in the assays. One Panel member commented on the absence of assays that examine the neurovascular unit, either individual cells or as a unit that significantly contributes not only to

almost all aspects of brain development and maturation but also to establishment of the blood brain barrier which is formed during gestation. Another Panel member mentioned the importance of metabolic differences during development and wondered if this could be captured by the battery.

The translation of the various assay endpoints to the *in vivo* manifestation of developmental neurotoxicity remains an issue of concern. Two Panel members strongly supported further research demonstrating a level of corroboration between *in vitro* assay effects and *in vivo* neurotoxicity to better understand the translational relevance from *in vitro* assays to *in vivo* manifestations of neurotoxicity and eventually to human health effects. Both aforementioned Panel members considered that critical questions remain on the applicability of these proposed *in vitro* assays as being representative of critical processes involved in nervous system development and on how well they might replace the *in vivo* rodent studies.

Recommendations:

Several Panel members identified challenges in providing feedback and questioned the readiness of the NAM battery for testing and assessment within the next year as the data for many endpoints will not be available until 2021 and not until 2023 for zebrafish behavioral studies. **Therefore, several Panel members recommended to postpone a final recommendation to a future scientific advisory panel once the data are available as this will weigh heavily on choices made.** Once the data are generated, the Panel acknowledged the importance to compare the results of the whole integrated testing battery with results from *in vivo* human and animal data. This is not meant to preclude the ability of the Agency to utilize all valid and relevant data in their efforts to determine risks for human health.

The Panel considered that any one NAM was insufficient for determining the potential for a chemical to cause neurotoxicity or developmental neurotoxicity. Rather, using a battery of tests with possible redundancies would be a better approach. The Agency asked the Panel to consider how the available data from NAMs may be used in current regulatory activities. In general, the Panel agreed that if the Agency uses published data in their evaluation, then there is no reason to exclude peer-reviewed published *in vitro* assay data - whether screening or mechanistic - in that final "weight of evidence." This could include neurotoxicity assays as well as other relevant published data as it corresponds to specific related biological processes. One point of consideration, however, would be to ensure that a sufficient sample size was included in any such publication.

All of the Panel members recommended that any battery be a “living and evolving process” that can be revised and improved with new technology, assays, information on validity and reliability and *in vivo* translation. One Panel member expressed concern that once a battery of assays is accepted for use in the regulatory arena, that there will be little “living process” and no incentive for developing new assays, refining endpoints, or establishing underlying mechanisms and biological processes involved. It was considered important to develop a robust base with critical evaluation and challenge including reproducibility and transferability between laboratories to avoid the mistakes and later-identified limitations of the DNT *in vivo* guideline studies. One Panel member recommended adopting the Bayesian Approach for this purpose and have it placed prominently in the “EPA Issue paper.” A reference was shared with additional

information on the step-by-step Bayesian calculation and numerous examples (McGrayne 2011). The Panel **recommended that the Agency take a leading role in ensuring this evolving, refining, living process to maximize the utility of the data obtained for regulatory decisions.**

This is not meant to preclude the ability of the Agency to utilize all valid and relevant data in their efforts to determine risks for human health.

Many Panel members recommended that any evaluation of the NAM data include transcriptional profiling, neurotransmitter profiling and measurements of other molecular markers as complements to better understand the biological plausibility of observed effects from the other assays.

Near-Term Actionable Items:

The various laboratories contributing to the NAMs for DNT have generated a large data set for evaluation. While there are efforts to review the data with expected results in 2021, there are specific types of information that will be relevant for any use of data by the EPA for weight of evidence. There was a notable absence of using the data available to conduct a power analysis to determine the number of observations required for confidence in any findings. It was confirmed by the Agency that such an analysis on each of the assay endpoints had not been conducted. The Panel recommended that EPA consider using their available data on control samples for a Power Analysis within any specific culture preparation and across culture preparations.
The Panel considered that further refinement in investigating statistical differences between treatments in these NAMs with *in vivo* endpoints was needed.

The Panel also recommended comparing data from existing *in vitro* screening efforts on uniform cellular responses (e.g., viability, proliferation, maturation) across multiple cell-based *in vitro* systems to develop criteria for identifying a chemical as neurotoxic versus cytotoxic.

Additional Panel Recommendations:

Further refinement in investigating statistical differences between treatments in these NAMs with *in vivo* endpoints is recommended.

Several Panel members were encouraged by the progress made in refining these assays and some thought that they would be useful for screening approaches. However, more work is needed to show that changes in isolated cultures are representative of *in vivo* effects. Efforts to evaluate the *in vitro* assays for their predictive validity of a “neurotoxic” effect in the developing brain are highly recommended and are considered by many Panel members as critical for the interpretation of the data for regulatory decisions. How representative are the endpoints of *in vivo* biological processes? The Panel noted the answer is “the *in vitro* assays are reasonably representative”, but the distance between *in vitro* models and *in vivo* nervous system remain large, and are a cause for concern and a focus of future effort.

Consider linking morphological endpoints *in vivo* with endpoints of effect at concentrations used in the *in vitro* assays. In risk assessment applications of toxicity data, considerable attention is applied in understanding the magnitude of uncertainty associated with inter- and intraspecies

variability. Two Panel members commented that there was uncertainty each time they used data collected at one level of biological organization to apply to another (i.e., going from cells to tissue, tissue to individual, and individual to populations). Since NAMs are missing tissue-to-tissue level interactions, it makes sense to also consider an Uncertainty Factor to go from cell/tissue-based responses to individual-level responses. These independent assay results could also be evaluated holistically. Consider an assay sensitivity approach to develop a value that would be protective of various endpoints as measured by various assay endpoints.

Establish a common agreement of what constitutes a neurotoxicological effect in the assays and if the thresholds of concern are considered clinically relevant.

Establish an approach that will be accepted to determine if the tested chemical concentrations reflect target tissue levels and how to integrate that into the evaluation.

In the Agency's presentation it was stated that "Decision makers need to understand what endpoint we're measuring, how it is measured, and how that relates to changes and neurodevelopment *in vivo*." The Panel agreed with the critical need for the decision makers to understand how the NAM endpoint relates to *in vivo* neurodevelopment. To this end the Panel recommended that the Agency actively participate in a collaborative effort to bring interested parties to the table for critical discussion on these assays and the proposed use and regulatory expectations. This would include those who have been actively developing the assays, those who will need to use the data, but also those with *in vivo* knowledge of developmental neurobiology, neuroanatomy, and neuropathology. If it is the goal of the Agency to be able to interpret the data within the framework of a neurotoxic effect and translate that to humans, a broader level of expertise and input is required.

Encourage the development and inclusion of glial based (astrocyte, oligodendrocyte and microglia) and neurovascular based targeted relevant NAMs.

In the EPA's Issue Paper on NAMs for DNT, one of the concerns and considered limitations of the *in vivo* DNT guideline study was "challenges associated with the study and its limited impact on human health risk assessments for pesticides". There are a number of concerns with this request for a direct association to reflect an ever-shifting over-expectation of the *in vivo* data set that are beyond what the basic biology would support and what the original drafters of the guidelines intended. Thus, to minimize the chances of this happening with the shift to NAMs, it is recommended that the Agency lay out the expectations of those making regulatory decisions and to determine if those expectations are well beyond the performance and information obtained from the assays.

Charge Question 4. – ***New Approach Methodologies for Developmental Neurotoxicity***

Question 4. Organophosphate pesticides share the ability to inhibit the acetylcholinesterase enzyme, which prevents the breakdown of acetylcholine leading to neurotoxicity. Inhibition of acetylcholinesterase is the basis of current OP human health risk assessments. In order to compare the relative sensitivity of the MEA NFA and HCI assay results to doses that inhibit acetylcholinesterase in laboratory animals, *in vitro* to *in vivo* extrapolation (or IVIVE) approaches were used to approximate NAM administered equivalent doses for a subset of

organophosphate pesticides as described in Section 2.3.6. *Please comment on the strengths and limitations of this comparison and whether there are alternative approaches for this evaluation using the available data.*

Strengths:

A Panel member noted the importance of toxicokinetic models that can bridge the gap between *in vitro* activity levels and external exposure levels and thus are key to providing EPA Office of Pesticide Programs with risk-based contexts for their policy decisions. The Panel member noted the following strengths: 1) the graphical presentations of the rat and human *in vivo to in vitro* extrapolation (IVIVE) comparisons were very useful visualizations of a lot of information; 2) the use of higher-quality models where available, with comparisons of HTTK and physiologically based pharmacokinetic (PBPK) models, was also a strength; 3) the modeling is generally well documented, with both the general and "simplifying" assumptions explicitly stated up front. The Panelist also outlined several weaknesses: 1) EPA did not address assumptions articulated for the IVIVE approach and HTTK modeling with respect to the organophosphates (OPs) case study; this weakness was identified by at least three Panel members; 2) The performance of the HTTK 3-compartment model was not articulated with respect to "fold-error" for the spectrum of test chemicals or specifically for OPs; model performance standards for differing purposes were not articulated; 3) One alternative approach was used for parameterization of hepatic intrinsic clearance (Cl_{int}); others exist; 4) The limited number of PBPK model comparisons could potentially be expanded.

One Panel member discussed recommendations for addressing weaknesses identified by the Panel. The same Panel member recommended re-examination of assumptions pertinent to assays performed and test chemical, as outlined in the following passages: The EPA appeared to be omitting the groundwork required to build confidence that the IVIVE strategy and tools chosen are applicable to the assay points of departure and pharmacokinetic models they propose to use. Quotes were taken from the US EPA (2020a):

General Assumption 1: "that a bioactive nominal *in vitro* assay concentration approximates the *in vivo* plasma concentration that would correspond to a similar effect." The EPA should weight the merits of using an interspecies uncertainty factor (UF) for pharmacodynamics prior to applying reverse dosimetry models to points of departure from NAMs relying on rat cells.
General Assumption 2: "that *in vivo* plasma concentration can be approximated based on steady-state kinetics." The EPA should assess the time to steady state for the members of this class of chemicals based on the available toxicokinetic literature, time course toxicokinetic models, and key physicochemical properties.
General Assumption 3: "that a toxicokinetic model to estimate external exposures…that may have resulted in that plasma concentration can be constructed using estimates of species-specific physiology and Phase I and Phase II enzyme-driven hepatic clearance." When species- and chemical specific metabolism rates are lacking, there are multiple approaches that could be used to generate an estimate. The EPA has chosen direct extrapolation from one species to another. At least two Panel members recommended that rat metabolism data be developed to facilitate comparisons of NAMs to rat *in vivo* data. When species and chemical specific *in vivo* or *in vitro* metabolism parameters are not available, the EPA should weigh the merits of the following alternative approaches based on the quality of the available data: 1) use a species-specific value

for a chemical deemed to be most structurally similar (e.g., similarity as identified using the EPA Chemicals Dashboard) (Lu et al., 2016); 2) use or develop a quantitative structure-activity relationship or quantitative property-property relationship for intrinsic hepatic clearance of structurally similar chemicals; 3) use a categorical approach to estimating typical rat/human clearance ratios for a class of compounds (e.g., similar to approach of Béliveau et al., 2005 for volatiles, based on hepatic Cytochrome P450 Family 2 Subfamily E Member 1 (CYP2E1) concentrations (though no consistent ratio is evident from the hepatic intrinsic clearance (Cl_{int}) values for OPs in the Supplemental Appendix for DNT-NAMs, Table 4).

Simplifying General Assumption #1. "100% bioavailability" by the oral route/portal vein. When applied to human safety assessment in IVIVE, this assumption is health protective. Empirical evidence supporting or refuting this assumption should be provided for members of the subject class of chemicals. Relying on this assumption to compare rat *in vitro* and *in vivo* effect levels has different implications—trying to perform best comparisons is different from making conservative policy assumptions. EPA should use a bioavailability predictor which would provide more relevant comparisons of *in vivo* data and predictions of external equivalents of *in vitro* effect levels.

Simplifying General Assumption #2. No extrahepatic metabolism. The only occurrence of the term "extrahepatic" in the EPA Issue Paper is at this location. EPA should summarize the potential for extrahepatic metabolism of OPs in relevant species and the impact of extrahepatic metabolism (if present) on a risk assessment.

Simplifying General Assumption #3. "Hepatic metabolism is first order (proportional to concentration) and does not saturate". This assumption is problematic if one is trying to use HTTK models for dose response assessment in rat studies, as traditional dose selection paradigms often put upper doses in the saturated realm. The EPA should evaluate the validity of this assumption for OPs in the range of NAM points of departure based on comparison.

Simplifying General Assumption #4. "Renal clearance is proportional to fraction unbound in plasma (Fup) and glomerular filtration rate (i.e. no active transport)." The EPA should evaluate available evidence supporting or refuting this assumption via literature searches for the chemical name and chemical class name and "active transport" (and other appropriate key words). If no data can be identified, it should be noted as data gap, and the implications for risk assessment delineated.

Simplifying General Assumption #5. "No biliary excretion or enterohepatic recirculation occurs." The EPA should evaluate this assumption for OPs because it is NOT a health protective assumption in the human.

A Panel member had some concerns about HTTK model performance and use of PBPK models, as discussed in the following: EPA states, "HTTK models have demonstrated reasonable accuracy" (Wambaugh et al., 2018). In the EPA Issue Paper, metrics for agreement are r^2 values. This metric was not appropriate as one can achieve high correlation (r^2) without high accuracy if all of the data are off by a similar relative amount in the same direction. The EPA should restate the model accuracy in terms of the fold error in the prediction (Wambaugh et al., 2018, Figure 9). Most chemicals were not "in the range" (i.e., within ~3x, or half an order of magnitude). The EPA should quantify the "fold error" performance of the 3-compartment HTTK model for each parameter (maximum concentration [Cmax] and area under the curve [AUC]), for all available data. The EPA should report the following statistics: % within 2-fold (World Health Organization International Programme on Chemical Safety, 2010 criterion), % within ½ log unit (3.16) (standard EPA interspecies toxicokinetic uncertainty factor), % within 1 log unit, the

range of fold error corresponding to 95% of the data, and % of data overpredicted. The EPA can then compare errors for the case study chemicals to the universe of HTTK-modeled chemicals. The EPA should avoid value judgements such as "reasonable" accuracy outside of the context of a specific risk assessment purpose, as desired/required level of accuracy differs from prioritizing functions vs. chemical specific risk assessments. At least two Panel members recommended that EPA should not generally use HTTK models for chemical-specific risk assessments.

One Panel member noted that the EPA generated comparisons of the outputs of multiple modeling assumptions which were in accordance to each other (rat vs. human intrinsic clearance). The standard of agreement that was established sets a lower expectation (agreement within ~3x or ~10x) and the numbers of comparisons lying within those ranges were not quantified. The EPA should compare HTTK model predictions to measured values instead of or in addition to their "rat to humanized rat" comparisons.

A Panel member noted that the EPA provided comparisons to PBPK models where such models were readily available. The lack of agreement between the PBPK and the HTTK models for two of three chemicals (US EPA 2020a, Figure 8) where comparisons could be made were not commensurate with their overall physiological and/or biochemical fidelity/accuracy for this class of chemicals. If additional comparisons can be made using the chlorpyrifos and diazinon PBPK models, that would add to the weight of evidence. The Agency stated that the chlorpyrifos PBPK model cannot be utilized because it was written in the PK software package acs1X (US EPA 2020a, page 62). The EPA should try to increase the number of HTTK to PBPK model comparisons. The EPA should pursue the following options: 1) Contract with people who are still using acslX for PBPK modeling. 2) Translate ACSL/acslX models to Magnolia or another platform. 3) Consider use of the diazinon PBPK model (Poet et al., 2004).

Another Panel member noted that the IVIVE approaches used for the calculation of NAM AEDs were consistent with the current state of the art for rapid evaluation of high throughput *in vitro* testing and are appropriate for use in the preliminary comparison with *in vivo* data on acetylcholinesterase inhibition described in the EPA Issue Paper. However, the same Panel member strongly recommended that, in the future, *in vitro* metabolism data be collected in the species of interest for the administered equivalent dose, rather than using available *in vitro* metabolism data from another species as a surrogate. That is, metabolism data in the rat should be used for the comparison with *in vivo* inhibition data in the rat, but metabolism data in the human should be used for calculation of Oral Equivalent Doses (OEDs) in the human. Although the comparisons of AUCs and Cmax's predicted using rat and human metabolism data suggested that they are strongly correlated, it also shows that the impact of differences in rat and human metabolism for a specific chemical can result in more than an order of magnitude difference in predicted NAM AEDs.

A different Panel member emphasized the importance of recognizing that the rapid screening HTTK IVIVE approach used for this comparison would be less appropriate for comparing alternative points of departure in a chemical-specific risk assessment. In support of a risk assessment, a more robust, quantitative IVIVE approach (Yoon et al., 2012) should be used. There are several simplifying assumptions associated with the HTTK modeling approach that were chosen to provide a conservative (health protective) bias for rapid model predictions of OEDs in the human to support early screening and prioritization. That is, the assumptions tend

to lead to a lower estimate of the OED or human equivalent concentration (HEC) AED that is associated with a given *in vitro* bioactive concentration. However, when estimating a point of departure for possible incorporation in a risk assessment, the desire would be to make assumptions that tend to lead to a more accurate estimate of the NAM AED. The comparison of the HTTK AEDs with PBPK AEDs for a few chemicals suggested that these conservative assumptions could result in substantial uncertainties in NAM AEDs. Of the simplifying assumptions used in the HTTK model, the ones that have the greatest impact on a NAM AED are:

100% Oral absorption: Pharma has developed an empirical approach for estimating absorption of drugs using data from human epithelial colorectal adenocarcinoma CACO-2 cells and *in vivo* studies, however, since it was based only on data for drugs, it was not generally applicable for environmental chemicals, which have a much broader range of physico-chemical properties.

Pre-systemic metabolism in the intestinal tissues can be ignored: This assumption is often incorrect for oral exposures because the cells lining the intestines possess significant metabolic capability. Because of the significant impact of intestinal metabolism on drug delivery, pharma routinely includes intestinal oxidative cytochrome P450 (CYP) metabolism in their IVIVE predictions by using CYP isoform abundance data in PBPK modeling platforms like SimCyp.

Metabolism in systemic tissues other than the liver can be ignored: While the liver provides the vast majority of systemic CYP metabolism capability, significant esterase metabolism capability was present in other tissues and in the plasma (particularly in the rodent). In the case of organophosphates (and many environmental esters), ignoring both plasma and intestinal esterases can seriously underestimate clearance.

Metabolic clearance is linear: This assumption is appropriate when the model is being applied at exposures that are sufficiently low to avoid saturation of metabolic processes, and is routinely applied when modeling the environmental (but not occupational) exposure levels typically anticipated for the human population or when calculating HEDs from *in vitro* bioactive concentrations.

Only the unbound fraction of the chemical in the plasma is available for metabolism in the liver (a.k.a., restrictive clearance): This assumption is incorrect in principal (because it ignores Le Chatelier's principle that an equilibrium shifts in the direction of product when product is removed), but it has nevertheless been used by pharma as a convenience. However, it has been demonstrated that the alternative assumption that all of the chemical in the blood is available for metabolism (non-restrictive clearance) results in a more accurate prediction of *in vivo* clearance (and the resulting steady-state *in vivo* concentrations) for chemicals in Toxcast (Wetmore et al., 2012), and this is the assumption that has generally been used in PBPK models for environmental contaminants and pesticides.

Renal clearance is by glomerular filtration of unbound chemical: This assumption is usually acceptable, but it is incorrect for chemicals like perfluoro-octanoic acid, that are retained by a saturable resorption process.

No biliary excretion or enterohepatic recirculation occurs: There is currently no way to address this concern in the absence of *in vivo* pharmacokinetic data, but it is not likely to be as important an assumption as the others listed above.

A Panel member recommended that these simplifying assumptions in HTTK modeling should be re-assessed to identify whether different assumption and additional chemical-specific *in vitro* data would improve the accuracy of the NAM AED estimates, and to determine potential approaches for their more accurate application in chemical-specific risk assessments. For

example, incorporation of saturable liver, intestinal and plasma metabolism would only require *in vitro* assays, and together with the use of non-restrictive clearance would greatly improve the accuracy of NAM AED predictions. The Panelist pointed out that these issues were currently under study in an ongoing research effort being conducted under the Cosmetics Europe Long Range Research Strategy, in which the US EPA ORD is participating. One of the goals of this effort is to develop internal Thresholds of Toxicological Concern for use in the safety assessment of cosmetics (Ellison et al., 2019). The European Commission's Joint Research Centre and US EPA ORD are also participating in this effort, in which the objective is to develop appropriate approaches for estimating conservative (lower) estimates of the steady-state blood concentrations associated with dosing in the animal studies. These animals studies served as the basis for the development of threshold of toxicological concern (TTCs), in order to be able to apply the TTC concept to inhalation and dermal exposures in humans. The Panelist recommended that the US EPA Office of Pesticide Programs (OPP) take advantage of ORD's involvement in this research to determine the appropriate values in improving pesticide risk assessment.

A Panel member commented that when using the highly conservative HTTK model, the NAM AEDs were substantially higher than the *in vivo* doses associated with AChE enzyme inhibition. Moreover, NAM AEDs calculated with PBPK models were even higher than those obtained with the HTTK model. As a result, supporting an inference that the effects observed in the *in vitro* assay occurred at higher concentrations than those associated with AChE inhibition. However, the same Panel member pointed out an important uncertainty that needs to be considered before drawing this conclusion: the reliance on nominal concentration to characterize cell and tissue exposures in the *in vitro* assays. The same member also noted that although chemical kinetics and free concentration have typically not been considered by the pharmaceutical ("pharma") industry when conducting *in vitro* screening of drug candidates, pharma is typically satisfied with qualitative rather than quantitative predictions. Moreover, greater challenges have been encountered with environmental compounds, primarily due to their wider range of chemical properties and more diverse array of exposure scenarios compared to drugs. The same Panel member continued to note that one of the chief limitations of *in vitro* assays identified in the evaluations was insufficient data defining the chemical domain of applicability of an assay which was intended for use with environmental chemicals. The assays had been validated using only drugs. Another Panel member commented that binding of a chemical to proteins/lipids in the media and to materials in the exposure system can be a key determinant of free concentration. Additionally, it was one of the crucial considerations for a successful IVIVE due to binding limits compounding the availability for uptake into cells and tissues *in vitro*; therefore the free concentration must be determined in order to accurately determine the *in vivo* plasma concentration that would be expected to elicit a target-tissue response similar to the cellular response in the *in vitro* assay (Birch et al., 2019; Groothuis et al., 2015, 2019; Kramer et al., 2012, 2015). The Panel member stated that the potential inaccuracy associated with the use of nominal concentration has been an "inconvenient truth" that has been resisted for several decades due to the perceived cost and time associated with the necessary analytical chemistry, but that concern is no longer justified. The same Panel member strongly recommended that the EPA take steps to assure that *in vitro* NAMs are appropriately evaluated by measurement of the free concentrations of representative chemicals spanning the chemical space intended for the assay, under standard assay conditions.

A Panel member recommended adding chlorpyrifos-methyl to the OPs included in the case study to assure that all members of this class of insecticides currently-registered in the U.S. are evaluated with this new and promising approach to understanding the potential for neurodevelopmental toxicity of these chemicals. The same Panel member also offered the following comments: The EPA Issue Paper, Figure 7 presented a comparison of NAM-generated Administered AED50s and *in vivo* data-derived Benchmark Dose (BMD) values for most of the OPs evaluated in the MEA NFA and the HCI assay. The BMD values were derived from data in rats on AChE inhibition, primarily in red blood cells (RBCs), although such data also may have been collected in plasma and brain. These data currently serve as the primary source for the derivation of guidance values (e.g., oral reference doses (RfDs)) in the human health risk assessment of OP pesticides.

A Panel member mentioned that several Panel members noted that the graphical presentations of the rat and human *in vitro* to *in vivo* extrapolation (IVIVE) comparisons were very useful in visualizing an extensive amount of information. The discussion that followed the Agency's presentation on the NAM OP case study on Day 1 of the meeting was very helpful in clarifying what initially had been characterized by several Panel members as an apples and oranges comparison. The cautionary note is that one should not demand more of this information than it can convey at the present time.

Several Panel members commented that the scientific community currently struggles with the question as to whether neurodevelopmental effects of concern may be occurring at dose levels lower than the hazard guidance values based upon cholinesterase inhibition. It was noted that in the EPA Issue Paper, Figure 7 does not provide answers to this question at this time.
A Panel member noted that the EPA's risk assessment community generally interprets the lower confidence bound on benchmark dose corresponding to an *x*% increase in response (BMDL10) as a value equivalent to the historical No-Observable-Adverse-Effect level (NOAEL) and as the Point of Departure (POD) to which uncertainty factors can be applied to derive reference values such as the Reference Dose (RfD). This is, in fact, the practice of EPA's Office of Pesticide Programs when deriving both acute and chronic oral RfDs for all of the OPs for which there were adequate data to model the dose response for cholinesterase inhibition. In a few cases where this was not possible, OPP derived acute and chronic RfDs by applying uncertainty factors to the NOAELs identified in the most relevant studies.

A Panel member noted that the EPA's ORD scientists described, in some detail, how and why they derived AC50s and AED50s, acknowledging that they should not be interpreted currently as No-effect levels. The ORD noted that they are continuing to refine the technology and to work towards the goal of being able to characterize other benchmarks that may more closely represent a no-effect level so that the comparisons can be seen as equivalent. Only then can a judgment be made on whether hazard guidance values based upon cholinesterase inhibition are protective against neurodevelopmental effects of concern.

Another Panel member offered the following limitation to the IVIVE approach: 1) In sections 2.3.6.1 and 2.3.6.2, (US EPA, 2020), a number of simplifying assumptions are declared with little or no upfront justification. In section 2.3.6.1, a general assumption of the IVIVE approach was that a bioactive nominal *in vitro* assay concentration approximates an *in vivo* plasma concentration that would correspond to a similar effect. How true would this be for compounds

that need to traverse the blood brain barrier and may encounter specific transporters? This latter consideration could have quite an impact on uptake into the target tissue. In section 2.3.6.2, a major simplifying HTTK assumption of the IVIVE is the absence of extra-hepatic metabolism. This assumption would seem to be particularly misplaced with regard to organophosphates, which have well known interactions with plasma esterases, including paraoxonase (Ceron et al., 2014) and carboxylesterase (Talcott, 1979).

Another Panel member noted that organophosphates are only one very small group of chemicals with the possibility of causing developmental neurotoxicity. As a class, however, OPs have a common mechanism of action (inhibition of acetylcholinesterase), which was why OPs were used as a test case for IVIVE. The EPA reported that the study authors noted that some endpoints in the DNT-NAM panel were not selective and that some endpoints could not be obtained for some of the test OP compounds. However, considerable work was done to calculate approximate AEDs for the majority of OP compounds tested and to compare these to benchmark doses in both human and rats. Both PBPK-derived and HTTK-derived AED's were determined. However, at the time the report was written, data were not always available so this could not always be done in both species. Where it could, the AED's in both species were approximately similar and were generally higher than benchmark doses. With caveats noted by other members of the Panel, it appeared that the IVIVE approach was reasonable, and is likely to be helpful with DNT-NAM assay data, including MEA NFA and HCI assays.

Charge Question 5. – ***Data-derived Extrapolation Factor's Using In Vitro AChE Inhibition Data***

Question 5. *In vitro* acetylcholinesterase inhibition data have been generated for rats and humans to develop interspecies and intraspecies data-derived extrapolation factors (or DDEFs) for pharmacodynamics for 16 organophosphate compounds in accordance with the EPA's 2014 *Guidance for Applying Quantitative Data to Develop DDEFs for Interspecies and Intraspecies Extrapolation*. The studies are briefly described in Section 3.2 of the EPA Issue Paper and more details can be found in MRIDs 50773501 to 50773503. Please comment on the strengths and limitations of these data. *Please include in your comments a consideration of the study design and methods, appropriateness of the selected measures, sufficiency of reporting, and robustness of the in vitro acetylcholinesterase inhibition data, including sample size.*

STRENGTHS:

Evaluation of measurable event associated with central nervous system (CNS) toxicity.
Data developed to formulate DDEF values.
Original data were made available for evaluation.
Technically reliable measures of acetylcholinesterase inhibition (AChEI) were developed.
Experimental results available from relevant test species and humans.
Both sexes were evaluated.
Effort was made to address intraspecies variability through multiple samples.
Individual samples, not pools, were evaluated for humans.
Experimental design allowed for direct comparison of results between and among species.
Effort was expended to demonstrate statistical validity of derived values.
Evaluation of findings by multiple organizations.

Sufficient data appeared to have been collected to allow for a reanalysis to address some of the weaknesses identified below.

LIMITATIONS:

Red blood cell (RBC) AChE may not fully represent brain AChE.
Some uncertainty accompanies assigning AChEI results from RBC to brain enzyme.
Animal data were not generated in the susceptible lifestage.
The number of samples appeared insufficient to characterize human variability.
The number of samples appeared insufficient to characterize the central tendency of rat data.
The demographics of the human samples does not reflect population heterogeneity with respect to (e.g.) lifestage, age, ethnicity.
Animal samples were pooled, rather than individually analyzed.
The analysis of AChEI to derive the bimolecular rate constant was not consistent with DDEF guidance, precluding comparison of candidate DDEF values across a range of concentrations.
The range of organophosphate concentrations used was not compared to concentrations expected to be attained in exposed animals (at the point of departure) or humans.
AChEI may occur at concentrations low enough to escape detection.
AChEI data were not interpreted according to DDEF guidance.
Statistical analyses:

- Uncertainties in some parameters (e.g., k' estimates) were not consistently addressed
- Statistical Analysis System datasets do not include standard error estimates for input response variable, KAPP, resulting in residual uncertainty not being fully characterized
- Robustness was complicated by applying linear and non-linear methods to a reaction that is neither first order nor second order
- Reliance on Warning indications may carry more weight than is valid
- It was not clear that sufficient statistical treatment of outliners has been applied
- Intra-person variability (variability shown by multiple measures from the same individual) seems not to be accounted for in most of the analyses
- Sufficiency of Sample Size: There are issues with coefficient of variability that impact sample size acceptability which are discussed more completely below

RECOMMENDATIONS

1) Provide increased detail in explaining why acetylcholinesterase inhibition in red blood cells is representative of acetylcholinesterase inhibition in brain tissue. This should include a description of the data and interpretations applied to acetylcholine esterase in red blood cells and brain, as well as the molecular interaction and subsequent modification leading to inhibited enzyme.

2) Develop a sample pool (not a pooled sample) of humans more reflective of the human population, to include more individuals from specific racial and ethnic backgrounds, as well as humans from the susceptible (developing) lifestage.

3) Increase the sample size in rats to include not only more samples, but samples from the susceptible life stage (developing animals).

4) Conduct or present data that demonstrates that the inhibition potential for perhaps a subset of these OP chemicals is the same/similar in brain and red blood cells. This will be necessary to develop an increased level of confidence in findings from studies of red blood cells.

5) Present findings directly in context of the EPA's Data Derived Extrapolation Factors guidance (US EPA, 2014). This should include presentation of inhibition determined at multiple concentrations, and candidate DDEF values calculated for different concentrations; as well as a comparison of the concentrations studied in vitro to the concentrations of OP attained in animal studies at the animal in vivo point of departure as well as the doses/concentrations to which humans are expected to be exposed.

6) Increase the presentation and discussion of key statistical issues identified further in this report. Address the issues related to the statistical analysis including:

- Address, discuss, analyze uncertainties in statistical parameters evaluated.
- Include standard error estimates for all input response variables.
- Fully discuss issues related to impaired robustness introduced by applying linear and non-linear methods of analyses to a reaction that is neither first order nor second order.
- Decrease reliance on Warning indicators as a criterion for exclusion of model results.
- Increase the level of clarity regarding the statistical identification and exclusion of outlier data.
- Increase the level of clarity regarding documentation and explanation that measures of intra-person variability (uncertainty produced by demonstration of different measures of inhibition from replicate samples) is consistently accounted for in all analyses.
- Include a discussion of how the coefficient of variability impacts sample size, how such data were included in decisions of optimal sample size and the impact of coefficient of variability on the level of confidence that can be placed on the results.

COMMENTS:

Several areas of the analysis received particular attention during the review meeting. These included addressing concerns regarding:

- The extent to which the data interpretation followed the EPA's guidance
- The acceptability of the number of rat and human samples
- The acceptability of the lifestage of rat samples analyzed
- The acceptability of the breadth of human population covered by the human sample set
- The extent to which the analysis focused on the bimolecular rate constant
- Choice of model selection based on software error warnings
- Conclusions reached on the basis of the statistical analyses

Comments from one Panel member focused directly on the DDEF guidance, and emphasized key points relative to the present analysis, citing the importance of DDEF sections and subsections 2, 2.2, 2.4, 4.1, 4.1.2, 4.2, 4.2.1.4, 4.2.2.1 (US EPA, 2014). The same Panel member cited the EPA DDEF guidance differentiating *in vitro* measures from *in vivo* measures and indicating, "DDEF values for toxicodynamics (TD) may also be quantified as the ratio of *in vitro* concentrations

producing the same level of response." The Panel member reviewed DDEF toxicodynamic guidance, including the evaluation the concentration-response relationships in respective species and samples to determine whether nonlinearities in the underlying data set are present and which might influence the value of the DDEF TD factor when derived at different inhibitor concentrations. In advocating a comparison of DDEF values derived at multiple concentrations, the EPA guidance intends to guard against uncertainty produced by nonlinearities in data sets, the differential presence of nonlinearities in data sets under comparison and differences in the slope of the concentration-inhibition curves describing the inhibition function in (e.g.) species under comparison. Any of these factors would produce instability in the relationship between DDEF value and the response level at which the ratio of concentrations was determined. Indeed, such nonlinearity was observed at low levels of inhibition during the same Panel member's own evaluation of data presented for bensulide oxon. The Panelist indicated that data describing the relationship between OP concentration and the degree of inhibition are presented for study samples in cells A26 through G33 of the "summary" worksheets in excel files for individual samples, and presented the results of an example DDEF raw data spreadsheet calculation from one rat and one human (bensulide oxon).

The Panelist emphasized that the EPA's DDEF method (1) specifies "concentration" as the unit of measure, (2) advocates a comparison of in vitro study concentrations to tissue concentrations attained in animal studies at the risk assessment point of departure and (3) states that a presentation of the rationale and implications for choosing the response level used as the point of extrapolation should be developed. To the extent that the derived biochemical term, *ki* (the bimolecular constant), is a single value (a point estimate derived from an amalgamation of data from multiple times and multiple concentrations) and not a concentration, and reliance on *ki* precludes a more detailed analysis of concentration-response data as required by DDEF methodology, the use of *ki* in deriving DDEF values cannot be justified – its derivation quite likely includes data from concentrations that are widely divergent from those approximating concentrations producing the level of inhibition expected at the risk assessment point of departure and, further, include data from physiologically irrelevant and unjustified OP concentrations. A Panelist included an example analysis of DDEF calculation using data from one rat and one human to emphasize these points, demonstrating the value of data already developed to serve as the basis for DDEF derivation.

The same Panelist was of the opinion that the US EPA selected RBC AChEI as a surrogate for the critical effect substantially based on expediency and cost, relative to time and conservatism of the number of animals required to supply sufficient tissue for evaluation. This contention of inappropriate application of data from these samples was supported in US EPA 2020b which states that there are differences between RBC and brain AChE in the peripheral anionic site that can alter binding, resulting in differences in binding at the catalytic site of the enzyme. This memo also identified a potential impact of yet-unstudied post-translational modifications and changes in other allosteric sites outside the catalytic site that can also influence the binding of substrates. While it is presumed that AChE activity in the RBC is a suitable representation of AChE activity in the brain, few conclusive studies are available to support this contention. Short of a reliable comparison of RBC-brain AChE activity and inhibition potential, the use of RBC AChEI as a surrogate for brain AChEI might be acceptable in some situations (i.e., where a very low and perhaps not biologically adverse level of inhibition is used to determine a risk assessment point of departure), but is unsuitable for a more complex evaluation of variability.

While the experimental design and data presentation was sufficient to demonstrate empirical findings of concentration (and time-) dependent enzyme inhibition, some discussion focused on inter- and intraspecies comparison being made at the level of a derived value (the bimolecular rate constant), rather than empirically-observed concentration-dependent inhibition data. These discussions also focused on the intent of the DDEF guidance (sections noted above) to force a concentration-based presentation of not only toxicokinetic, but also toxicodynamic comparisons.

Multiple Panel members noted that the reporting was insufficient. One Panel member observed inconsistencies across the several submitted documents. A second Panel member remarked on the use of an incorrect term, while a third Panel member observed the lack of documentation that explained what was reported in the data files. One of these Panel members also questioned the robustness of the data (covered more fully below), indicating that uncertainty exists when, for example, a pseudo first order approach was taken to estimate the *ki* parameter for a reaction that was not in the first order.

A third Panel member concluded that the biochemical method used to determine AChE inhibition was appropriate but questioned several other aspects of the study. Selection of the most appropriate model on the basis of a Warning label over an AIC value prompted the Panelist to suggest that increasing the sample size might clear the Warning. Large variability (21-fold) among humans was noted for omethoate, with within-subject variability also noted as high (approximating 3-fold). Sample size was noted as being too small for some population groups (e.g., African Americans, Hispanics) to draw any meaningful conclusions. Pooling of rat samples by sex was criticized. The Panelist noted that there was little or no interpretation of the results in the Conclusions sections of the submitted reports.

One Panel member addressed variability of *ki* values, noting a range of variability generally in agreement with what might be expected from blood samples used for clinical evaluations; this same Panel member observed that "the overall range of rate constants for each OP compound tested was relatively small." Noting that a relatively low number of rats from a single strain was used in the analysis, the Panelist indicated that the need seems to be for more rat samples, rather than more human samples. Noting the value of concentration-response data, the same Panelist indicated that AChE inhibition may actually occur at concentrations that are orders of magnitude lower than those tested, perhaps even lower than traditional limits of detection.

<u>"Representativeness" and sample size</u>:
One Panel member introduced the term "representativeness" during the meeting discussions when articulating his concern that the human study did not adequately represent the human population, either in its sample size or the nature of population differences particularly, in age or race/ethnicity. Another Panel member pointed out that race and ethnicity appeared to be conflated and that one cannot automatically assume one from designation of the other. It was also noted that neither Native Americans nor Asians were represented at all.

There was a critical flaw in both the rat and the human study in the failure to adequately examine the impact/import of age on the outcome. The US EPA 2020b presented five hypotheses related to how pharmacodynamic parameters (PDPs) associated with AChE inhibition would compare across species (rat to human) and within species (human). Two of them (#3 and #4) posit

specifically that age, gender, or disease status would have no effect, either within or across species.

At least one Panel member found the argument that age has no impact on pharmacodynamics parameters (PDP) unconvincing pre-meeting, and was not convinced otherwise as a result of discussions at the meeting.

The Health Effects Division (HED) of the Office of Pesticide Programs frequently evaluates risk for the following U.S. population subgroups: all infants (<1 year old), children 1-2, children 3-5, children 6-12, youth 13-19, adults 20-49, females 13-49, and adults 50-99 years old. Females 13-49 are singled out for several reasons: they are of child-bearing age; they are the vehicle/surrogate for prenatal exposure; they are usually considered the most sensitive subpopulation in the occupational setting. Age groupings may be adjusted somewhat on a chemical-by-chemical basis, depending upon the specific exposure scenarios presented by the use patterns of the pesticide being evaluated.

So, how does this information affect an assessment of the design of the Data-derived Extrapolation Factors (DDEF) rat and human studies? It renders them both inadequate, but in somewhat different ways. With regard to the rat study, additional groups, representing younger life stages, should be included. Selection of which age group(s) should be tested can be informed by the designs for the Acute or Repeated or Gestational Comparative Cholinesterase Assays (CCA), non-guideline studies that have been required for OP parent compounds and some metabolites. In these assays, single or 10 daily repeated gavage doses are administered to neonatal (beginning postnatal day 11) and to young adult (e.g., postnatal day 58-63) rats of both sexes or to pregnant dams on gestation days 6-20 (three or four treatment groups and a control group). In the acute study, peak cholinesterase (ChE) inhibition in plasma (sometimes), red blood cell (RBC) and brain was measured 4 or 8 hours following dosing. Most often, the acute and repeated dose studies results show that the neonatal pups are more sensitive than the young adults (that is, they show effects at lower doses). However, none of these study designs allow for parsing any differences to pharmacokinetic (PK) or pharmacodynamic (PD) factors; either or both could play a role.

During the question clarification session following the presentation to the Panel of the results of the rat and human studies, several Panel members raised the issue of lack of representation of key age groups in one or both studies. One of the agency representatives asked what impact would it have on choosing to expand the rat study (or not) if one already knew the comparative sensitivities of the young versus adults, based upon the results of the CCA studies. As pointed out above, these *in vivo* studies do not allow for parsing any differences in the PK or PD contributing factors and thus would be of little use in deriving Data-derived Extrapolation Factors (DDEFs) for specific chemicals.

Turning to the human data, an N = 18 was simply not robust enough no matter how rigorous and tortuous the statistical analysis may be. Matching up current numbers of humans evaluated against the subpopulation groups generally assessed, one sees 4 newborns, but 0 older infants in the all infants (<1 year old) category, 0 in the children 1-2 category, 0 in the children 3-5 category, 4 in the children 6-12 group, 2 in the youth 13-19 group, 6 in the adults 20-49 group, 5 in the females 13-49 category, and 2 in the adults 50-99 year old group. Children in the 3-5 and

6-12 year old groups are frequently those assessed to be at greatest risk given their dietary and behavioral habits, exposures per unit body weight and active stages of neurodevelopment. It would be particularly important to have them represented in the sampling. At least two Panel members argued that a sample size at least 60-80 individuals, appropriately spread across age, gender and race/ethnicity groups, was warranted.

A Panel member noted lack of defined section addressing the developmental maturation aspect of the studied enzyme in blood and brain and recommended inclusion of documentation of the assumptions supporting the reliance of data from RBC AChEI as representative of how each organophosphate will reach and react with brain enzyme. Such a discussion should also include whether there are known mutations that might affect AChE function.

Sufficiency of sample size:

The parameter of interest in this study was the interspecies pharmacodynamic DDEF (denoted as EF_{AD}) which is estimated by the ratio.

$$EF_{AD} = k_{i,Human} / \ k_{i\_Rat}$$

While estimated k_i values are available for individuals, EF_{AD} was estimated as the ratio of the mean of the $k_{i,Human}$ from the human samples, and the mean of the k_{i_Rat} for the rat samples.

In the EPA Issue Paper, page 72, the Panel found that Exponent "provided normal Q-Q plots of the *ki* values and the ln (*ki*) values to support rationale for assuming the *ki* values were lognormally distributed for all chemicals." The EPA Issue Paper and the EPA Coversheet and ICF Statistical Analysis assumed EF_{AD} was lognormally distributed. One Panel member ran simulation of ratios of lognormally distributed random values to show that in fact EF_{AD} was adequately characterized by a lognormal distribution.

Both of these means could be assumed to be normally distributed with variability between individuals. In addition, there is variability in estimation of the k_i for an individual (within variability) (topic of Charge Question 8). It seems that within variability is not accounted for in most of the analyses.

Sample size can be estimated a number of ways, depending on how the precision target is specified.

The *Exponent sample size calculation memo* specifies a sample size determination approach that is based on a test the coefficient of variation, CV, defined as CV = s/m where one assumes that m = true (EF_{AD}) and s = standard deviation (EF_{AD}). The CV test is described in Banik et al. (2012). The test hypothesis is

H_0: CV =CV_0 versus H_a: CV > CV_0

The test statistic used is from Miller (1991) and depends on an assumption of normality and the asymptotic distribution of the sample CV. Let CVe be the estimated CV.

Then the test statistic M defined as $(CVe - CV_0)/S_{CVe}$ has a standard normal distribution where S_{CVe} is defined as the sqrt$\{(CVe^4 + 0.5CVe^2)/n\}$.

This test has the benefit of not having to specify a variance term but to rely only on the estimated value of the CV and the target difference, d_{cv}, between the observed and expected CV. Note that the Banik et al. (2012) paper also describes a test statistic by Sharma and Krishna (1994) that is more robust to the assumption of normality and which can more easily be solved directly for n given d_{cv} and the given Type I error rate, a.

Exponent in their sample size justification, set the sample size at n=18, and computed the value of ECV that would be statistically significant at a = 0.05 for a range of potential true CV values [5%, 10%, 20% and 30%] and with this computed the corresponding effective detectable difference, d_{cv}, of true population variability considered as a percent.

The computations in the Exponent sample size calculation memo were able to be confirmed. Hence a sample size of 18 is reasonable if an accuracy of ±2% is acceptable if the true CV is about 5, or ± 14% if the true CV is 30%.

Note that the Miller (1991) test statistics can be solved for *n* similar to what is done for the sample size based on specification of relative error. In this case, with type I error a specified and type II error b specified and prespecified CV target of d_{cv}, the sample size is:

$$n = (Z_a + Z_b)^2 [CVe^4 + 0.5\ CVe^2]/\ d_{cv}^2$$

For a true CV of 30%, and a difference of dcv = 14%, Type I error of 0.05, Type II error of .3, the computed n is 79 (not 18). This suggested that the power of a test to detect a 14% difference between the observed and expected CV when the true CV is 30%. at a type I error of 0.05 must be quite low (actually somewhere around power = 0.1 meaning a 0.9 probability of experiencing a type II error).

Charge Question 6. – ***Data-derived Extrapolation Factor's Using In Vitro AChE Inhibition Data***

Question 6. Given the structure of correlated data, nonlinear mixed-effects models were used to analyze the *in vitro* inhibition data in order to calculate the interspecies and intraspecies pharmacodynamic DDEFs as described in Section 3.2 of the Agency's Issue Paper and MRID 51182301. The ratios of the biomolecular rate constants between species or subpopulation were estimated from the nonlinear mixed-effects models, which are reported in Section 3.3 of the Agency's Issue Paper and MRID number 51182301. For a number of chemical-specific datasets analyzed by Exponent, the fitted non-linear mixed model generated warning statements due to a full rank final Hessian matrix. Additionally, for several of the chemical-specific datasets analyzed, visual evaluation of diagnostic plots revealed severe outliers or a severe imbalance in the distribution of residuals, leading to questionable model fit. In an attempt to resolve the warning statements and outlier issues,

the EPA consulted with its statistical contractor at ICF, which submitted a supplemental analysis (see the EPA Coversheet and ICF Statistical Analysis).

a. Please comment on the methods or techniques employed by Exponent using the nonlinear mixed-effects models.

b. Please comment on any concerns associated with the warning statements and model-fit issues. Taking into consideration the supplemental ICF analysis to address these issues, suggest, if necessary, other methods or techniques that could be suggested for addressing such warning statements and model-fit issues.

Methods used in the nonlinear mixed-effects models:

The approach to model-fitting is described on pages 11-13 of Higgins et al., 2020. The Panel concluded that the approach to model-fitting described in the Agency Issue Paper (US EPA 2020a) represents current good statistical practice and seems well thought out. Use of AIC is a typical measure used to choose among different models. Graphical diagnostics are used extensively to supplement AIC in final model selection.

The SAS NLMIXED procedure is used throughout this analysis to fit these models. Default values are chosen for all NLMIXED statement options except for some scenarios where specific options are reset to help improve convergence.

The SAS code aligns with the description provided in the Agency Issue Paper (US EPA 2020a) but includes few comment statements other than indicating which scenario is being addressed and which model is being fit. Justifications are not provided for why default model fitting options are changed for the model being fit. The logic and/or analysis approach is not presented or documented but has to be inferred by looking at which fit options have been changed from the defaults.

One Panel member referred back to the discussion of the k_{app} response variable in a previous question and recommended that the analysis start with the raw measurement that are output from laboratory experiments. This allows estimation and propagation of uncertainty in the k_{app} slope values through to the final DDEF estimates.

Recommendation: In estimating k_i, the analysis should be performed on the experimental time course measurements rather than on k_{app} values derived from regressions on individual time course measurements.

Concerns associated with model-fit issues:

The methodology described in the Agency Issue Paper (US EPA 2020a) uses the entire set of k_{app} (derived) values from individual humans and pooled rat samples to produce k_i estimates with preferred statistical properties as well as pooled estimates of residual variability. This approach is better than fitting the nonlinear model separately to the individual samples or simply using a

(fixed effects) nonlinear regression approach. Proc NLMIXED incorporates empirical Bayes estimation methodology to produce estimates for the k_i. This method produces quite good estimates for the mean k_i for humans and for rats, but the individual k_i estimates have the property that extreme values are closer to the mean than would be the case with traditional nonlinear regression (e.g. are "shrinkage estimates"). The ramifications of using shrinkage estimates when estimating the upper 95th percentile of the population, and with this statistic also estimating the ratio that makes up the intra-species DDEF are not discussed.

One Panel member commented that the issue with using an empirical Bayes approach is that the prior is constructed from the data, vs a truly Bayesian approach in which the priors are specified without consideration of the data. So, in an empirical Bayesian approach the data are used twice: to specify the mean/center of the prior (sometimes maybe even the variance) and to derive the posterior. A truly Bayesian approach would build the prior based on information external to the data. It is concerning that by using an empirical approach not only are the estimates shrunk towards a mean, but there is no opportunity to combine the external information represented by a true prior and the information available in the specific data under consideration. That said, empirical Bayesian estimators are used often. The EPA should investigate other approaches, such as using true Bayesian priors that may facilitate better quantification of uncertainty.

Recommendation: Consider assigning true Bayesian priors to better quantify the uncertainty in k_i estimates.

The model-fit issue is discussed on page 14 of MRID 51182301 (2020).

> "Model warnings were generated in some cases due to a full rank final Hessian matrix (SAS warning: "WARNING: The final Hessian matrix is full rank but has at least one negative eigenvalue. Second-order optimality condition violated"). This warning occurs when the model does not fully converge, which adds uncertainty to the estimates. If the final model selected based on AIC value had a warning statement but the alternative final model did not have a warning statement, the alternative model without the warning was selected as the final model. If both final models 2 and 3 had SAS warning statements (i.e., model fit issue), the final model was selected based on a smaller AIC value, but the results of the selected final model should be interpreted with caution."

The approach to handling the SAS warning outlined in the quote above is reasonable and represents good statistical practice. But SAS© offers some suggestions for what to do when the model does not fully converge. Since Proc NLMIXED is strongly related to Proc MIXED, some of the many points discussed in the SAS Proc MIXED manual[1] on page 6167 should be considered. It is clear that the ICF analysts incorporated several of the suggested "fixes" in their analyses, for example the use of parameter scaling, setting the max iterations higher, and the use of ridge scaling of the likelihood surface.

It is not clear that other potentially useful approaches were attempted. Particularly of note is the statement in the SAS MIXED manual that "A nonpositive definite Hessian matrix can indicate a

[1] https://support.sas.com/documentation/onlinedoc/stat/141/mixed.pdf

surface saddle point or linear dependencies among the parameters." (page 6168 of the online SAS MIXED manual[1]).

The potential for linear dependences among the parameters suggested that the model may be formulated in a way that makes it difficult to find the maximum of the likelihood surface, or that there is just not enough data to estimate the particular covariance structure selected. This latter should be examined more closely.

For example, in the fit of all the data for the chemical compound Terbufos oxon sulfoxide the final model chosen is Model 3, but the final covariance estimates are quite close to the initial values and standard errors for these parameter estimate are not provided. This suggested that the model may have been over specified and potentially Model 2 should have been considered. The analysis protocol tells us that that Model 2 was considered. The fact that it is not the final model suggests that it also had an issue with its fit and it may also have been over specified. Model 2 without the covariance term and Model 3 without covariance terms should have been fit and compared to the two models with covariance terms. In the model fit for other scenarios, the final variance and covariance terms are not statistically different from zero. This is another situation where a reduction in the covariance structure should be examined.

In many scenarios, not enough variation in the observations above the "residual" variation may be available to facilitate also estimating the covariance parameters. Here again, stepping down the complexity of the covariance matrix is a reasonable next step. That is, entertain a model where the term for the covariance between A and B is assumed known and equal to zero.

Recommendation: For scenarios where the initial estimate for the covariance between A and B is close to or equal to zero, consider fitting a model where the assumed covariance is zero.

Reparameterization of the covariance matrix is another option not examined. Rather than specify the covariance directly (the *grab*, *grhb* terms), the covariance can be specified as the correlation times the standard deviations, that is *grab = corrab * sqrt(gra*grb)*, and the model asked to estimate the correlation. Another approach is to parameterize the variance terms on a log scale in which case the final values can never be at or below zero. That is, setting for example *var(rra) = exp(gra)*. The final estimate may still be quite small when all is said and done, but the final estimate will not be zero.

The SAS warning of non-convergence, which the Panel recognizes occurs seldom in this analysis, suggested the potential that the final estimates are derived not for a global maximum of the likelihood surface but for a saddle point in the likelihood surface. Evidence for this can be developed by starting the model fitting process from different initial parameter values. Varying the starting values may allow the search algorithm to eventually escape the saddle point to find the global maximum. If the final estimates are the same as before it may still be a saddle point. This is a good next step for those scenarios where the final covariance parameter estimates are not vastly different from the initial input values.

Note that SAS Proc NLMIXED has many options that allow the analyst to exert fine control of many aspects of the likelihood search process. Some that might be explored include DIAHES (a

SAS control parameter)– using only the diagonal of the Hessian matrix and RESTART=*i* – specifying that the search direction be reassessed after *i* iterations. Many other options should be explored before accepting the estimates from questionable fits.

There is no guarantee that any of the models considered for a scenario will be adequate. This is particularly the case when the data may be too sparse to adequately estimate model parameters. This issue is also discussed in Questions 5 and 7 where the impact of dividing the full data set into smaller groups for the intra-species analysis are considered.

The issue of severe outliers is more difficult to assess. In Proc NLMIXED, predicted values are computed using the parameter estimates and empirical Bayes estimates of the random effects. Standard errors of prediction are also computed and output when requested in the PREDICT OUT = statement. Since the details of the macro used to produce the residual plots was not provided in the supplemental materials, it is assumed that the residuals examined in the outlier analysis are simply the difference between the observed and predicted values of PRED (a SAS control parameter). An alternative would be to use the standard errors of the predicted values to "standardize" the residuals before being assessed. It may be that those residuals that appear outliers are actually from predictions with high uncertainty. The ICF reanalysis computed and plotted these standardized residuals to demonstrate that this in fact was the situation, with many of the residuals originally identified as outliers.

For some scenarios the outlier issue reflects the fact that the underlying data do not fully line up with the assumptions of the model. The model assumes, for example, that the phosphorylation constant {A} and the dissociation constant {B} are assumed (bivariate) normally distributed. Consider, for example, the individual sample curves provided in the supplemental files of the model fits for the chemical Naled for the rat/human scenario. The rat individual sample curves show two "groups" of responses, two in one group (high A, low B), four in the other group (low A, high B). The human sample curves display a longer low-end tail for the upper asymptotes (the estimates of A) that suggest a more lognormal shape to their distribution. This finding supports the need to consider correlation between A and B in the model although estimating a non-zero value for the correlation is not always guaranteed. While the nonlinear mixed effects regression model is likely to do a good job of estimating the parameters, there is no guarantee that the estimates for A and B effects will truly be normally distributed which may be reflected in plots of the A and B effects as well as in the estimated residuals.

As described in a similar discussion in charge question 5, a Panel member noted that the term "biomolecular rate constant," is a typo seen on line one of Section 3.2.1 in the EPA Issue Paper as well as in other places in the earlier version of the Charge Questions, also shows up on line 4 of this Charge Question. MRID 50773501 (MSU 2018) and MRID 50773503 (Chambers et al., 2018) also reference the term, "bimolecular rate constant". Because this constant plays a central role in the risk assessment, it is recommended that EPA discuss the meaning and significance of this constant when it first appears in Section 3.2.1. Inserting a sentence with references inserted on line 3 under Section 3.2.1 before the word "Briefly" as demonstrated below would help readers of the Issue Paper (US EPA 2020a) better appreciate the importance of this constant.

> "The bimolecular rate constant k_i, a measure of the inhibitory power of an organophosphate and comprised of both the binding affinity to the active site and rate

of phosphorylation (Coban et al., 2016), was originally derived and discussed in Main (1964)."

In Sections 3.2.1 and 3.2.2 of the EPA Issue Paper (US EPA 2020a), three sets of constants, the bimolecular rate constant, the phosphorylation constant, and the dissociation constant, are discussed. Across the Mississippi State study reports these three constants are designated, respectively, as ki, kp, and KI. In Section 3.2.2, the SAS analyses uses KAPP, A, and B. The graph of the Hyperbolic Plot uses k', k2, and kd, respectively. Without further clarification and explanation, the multiple terms for the same quantity is very confusing to readers. The EPA should harmonize notation for this constant in these sections to reduce reader confusion.

Charge Question 7. – ***Data-derived Extrapolation Factor's Using In Vitro AChE Inhibition Data***

Question 7. For the intra-species analyses, Exponent conducted stratified analyses, where the 18 human samples were subset into smaller groups to estimate the bimolecular rate constant ratios for these subgroups as described briefly in Sections 3.2 and 3.3 of the Agency's Issue Paper, with more details provided in MRID 51182301. EPA has concerns about the reliability of these stratified analyses due to the small sample sizes of the subgroups, as well as concerns with warning statements and outliers. EPA's statistical contractor, ICF, provided a supplemental analysis to address the warning statement and outlier issues (see EPA Coversheet and ICF Statistical Analysis). *Please comment on these intraspecies analyses performed by Exponent and their utility to evaluate intraspecies human variability in response to organophosphate exposure taking into consideration the sample sizes and the supplemental ICF analysis.*

The document "*Guidance for applying quantitative data to develop data-derived extrapolation factors for interspecies and intraspecies extrapolation"* (US EPA, 2014) indicates on page 33 two approaches to characterize intra-human variability: a first approach based on a unimodal analysis, and a second approach based on a bimodal analysis. A unimodal analysis was performed when it was not possible to identify a priori a subpopulation of sensitive individuals on the basis of physiological, biochemical or life stage-attributes. On the other hand, a bimodal analysis was used when a subpopulation of sensitive individuals can be identified. In this latter case, to derive an extrapolation factor, it was necessary to compare the central tendency in the dose metric for the general population with the central tendency in the dose metric for the subpopulation of sensitive individuals.

To quantify intrahuman variability in the bimolecular rate constant k_i, Exponent performed both types of analyses, unimodal and bimodal.

In providing an answer to this charge question, the Panel discussed both analyses, however as the charge question refers more specifically to stratified analyses, in their answer, Panel members focused particularly on the bimodal analyses.

All Panel members shared concerns similar to those expressed by the Agency regarding the reliability of the analyses' results due to the small sample sizes. Multiple Panel members pointed out the limited availability of data for certain ethnic and racial groups, and reiterated the absence

of subjects of Asian descent in the dataset despite a probably adequate sample size for Caucasian subjects. All Panel members recognized the repercussions of the small sample size in terms of statistical inference and model fitting, including convergence problems, standard errors estimated to be equal to zero, and extreme outliers (see the range of biomolecular constant values k_i values for malaoxon and omethoate). In addition, while Panel members recognized and valued the supplemental efforts of the statistical contractor, ICF, to address some of the model fitting issues, several members of the Panel agreed with the statement that ``[..] these subpopulation analyses need to be interpreted with caution [..]'' (Higgins et al., 2020, page 8).

Multiple Panel members recommended that more human blood samples be added to the already collected blood samples in an effort to increase and more effectively characterize human sample variability. The same Panel members indicated the fact that ongoing work in this direction is slated to occur at Mississippi State University under the sponsorship of a consortium of companies, as indicated in the document "*Supplemental statistical analysis of Organophosphorus (OP) pesticides in vitro inhibition study*" by Exponent, 2020 (page 35).

On the topic of samples representativeness of the human population, one Panel member offered the following comparison between the demographics distribution in the human samples and the demographics of the US general population: while adults 16-60 years of age make up about 50% of the human sample, they account for 59% of the US general population, thus highlighting the under-representation of adults in the sample. On the opposite side, the same Panel member noted an over-representation in the sample of juveniles (samples of 10-13 years of age) and infant (cord blood samples): whereas they constitute 28% (for juveniles) and 22% of the sample (cord blood), respectively, only 13% and 0.06% of the US population has an age between 10 and 19 years of age and between 0 and 5 years of age. The Panel member estimated the US general population demographics break down from the one year estimates derived from the American Community Survey of the US Census Bureau, and derived the expected percentage of the US population that was less than 6-months old as one tenth of the estimated number of US children below 5-years of age. The same Panel member noticed no significant discrepancies between the sample and the US general population in terms of gender and race: 44% of the blood samples belong to males versus 49% of the US general population was male; analogously, the percentage of white subjects in the sample was 72%, versus a proportion of 76% for the US general population.

Because of the over-representation of children and cord blood in the sample, the abovementioned Panel member argued that the distribution of bimolecular rate constants k_i would be more representative of children and cord blood k_i values than the general US population, impacting measures of central tendency as well as measures of variability, such as the standard deviation. Particularly, the Panel member observed that if the bimolecular rate constant k_i tends to be smaller for children and cord blood, then the mean and standard deviation of the sample k_i 's would also be smaller than expected. The same Panel member offered a recommendation to account for the disproportionate representation of juvenile and cord blood in the estimation of the Data-Derived Extrapolation Factor (DDEF). Specifically, the Panel member recommended either using a resampling approach with sampling weights that reflect the demographic distribution in the US general population or simply a computation of the weighted geometric mean and corresponding standard deviation. The Panel member noted that in applying the resampling strategy on the data provided, no significant difference was noted in terms of DDEF values, very

likely due to the fact that the bimolecular rate constants k_i for juveniles and cord blood in the sample tend to be very similar to those of adults.

Two Panel members observed a large range of variability in bimolecular rate constant k_i across organophosphate compounds, and another Panel member recommended that insights and more documentation regarding the extent of the difference be reported in documentation.
A Panel member noted particularly a large variability in terms of bimolecular rate constant k_i for Naled. The same Panel member remarked that some variability in the data relative to Naled could be explained by differences in solution and water content in the DMSO used to aliquot Naled. This, in turn could affect stability of storage or Naled's activation once in aqueous suspension. The Panel member also noted that some of the variability in the bimolecular rate constant k_i could be ascribed to the fact that volatile trifluoromethyl ketones are mobile on a 96-well plate, causing inhibition in adjacent wells, as also observed by Camerino et al. (2015).

Although not discussed in the charge question, some Panel members offered comments regarding the estimation of intrahuman variability performed by Exponent using a unimodal analysis approach, where the intraspecies extrapolation human toxicodynamic (TD) factor was derived as the ratio of the 97.5th, respectively, 90th, 95th, 99th percentile and the mean bimolecular rate constant in the general population. A Panel member indicated difficulties understanding how the upper percentiles for the lognormally distributed bimolecular rate constant k_i values were computed. The same Panel member also indicated an inability to replicate the calculation used to derive the Data-Derived Extrapolation Factors presented in Table 16 of the EPA Issue Paper (US EPA 2020a). The Panel member recommended that a different approach be used to estimate the bimolecular rate constant values, k_i if they are indeed assumed to be lognormally distributed: in particular, the Panel member referred the Agency and Exponent to the estimation procedures outlined in chapter 13 of Gilbert (1987).

A second Panel member elaborated that while the Panel member understands conceptually the approach undertaken to derive the intraspecies extrapolation human toxicodynamic (TD) factor, the approach currently used by Exponent does not reflect the fact that the values of the bimolecular rate constant *ki* are not known for each human, and that the estimates obtained from the PROC NLMIXED output are just estimates. The same Panel member recommended that this uncertainty was quantified and accounted for, through the use of, for example, a bootstrap approach.

Charge Question 8. – ***Data-derived Extrapolation Factor's Using In Vitro AChE Inhibition Data***

Question 8. For intraspecies analyses, a limited subset of chemicals had three replicate analytical results on each of the four sources of human samples. The results from these analyses were used by Exponent to characterize the total variability of the estimates in terms of experimental variability and subject variability as described briefly in Sections 3.2 and 3.3 of the Agency Issue Paper with more details provided in MRID 51182301. The results were not consistent across the

chemicals, ranging from 3% to 84% of the total variability due to differences in the replicate analyses.

a. Please comment on the utility of these analyses to characterize human variability in response to organophosphate exposure.

b. If there is utility in generating these data for additional OPs, please provide any suggestions for improving the design and conduct of the study.

Members of the panel recognized the effort undertaken by Exponent to gain a better understanding about the sources of variation in the human bimolecular rate constant k_i. The analyses performed by Exponent using replicate data were conducted with the goal of partitioning the overall variability of the bimolecular rate constant k_i into experimental and intra-human variability.

In assessing the utility of these additional analyses, some members of the Panel noted that even though replicate data was available, it was only available for four subjects and three chemicals. Although a Panel member noted that the data used in this set of analyses represent an improvement over previous efforts, particularly when considering the entire sample of 18 subjects, consisting of subjects of different age, gender and ethnicity, two Panel members remarked that 4 subjects are not enough to characterize the variability among humans nor to draw definitive conclusions. These two Panel members deemed the analyses performed using replicate data of limited utility.

Another Panel member found the replicate data analyses useful, particularly if considered as the beginning of a New Approach Methodology, where new data can be incorporated sequentially within each new analysis in a Bayesian framework implemented via Markov Chain Monte Carlo. As an example, the Panel member recommended the incorporation of other human data collected in similar experiments by Dr. Chamber's group. The same Panel member also envisioned the possibility of creating new synthetic data through a Monte Carlo approach, sampling data values from the estimated probability distributions of already existing human data.

Other Panel members indicated that even though, from a conceptual point of view, using replicate data to understand the amount of experimental and intra-human variability in the bimolecular rate constant k_i represented the right approach and it could be potentially useful, the implementation of the repeated analyses had some weaknesses.

As a first point of concern, one Panel member noted a difference in the procedures used to derive the bimolecular rate constants k_i used in the replicate analyses versus the procedure implemented to derive the k_i used in the interspecies and intraspecies data analyses. Specifically, the same Panel member indicated that while in the document Higgins et al. (2020), it was stated that the bimolecular rate constants k_i in the replicate analyses were estimated by fitting a hyperbolic model to the AChE phosphorylation rate data available for each individual sample (Exponent, 2020; page 75), in the interspecies and intraspecies analyses the bimolecular rate constants were estimated by fitting a joint non-linear mixed model to both human and rat data using PROC NLMIXED in SAS (Higgins et al., 2020; pages 11-15). Due to differences in procedures, the

Panel member recommended care in comparing estimates of variability across the two set of analyses for each of the three organophosphates.

Having estimated the bimolecular rate constants k_i for each human subject with replicate data, Exponent fitted linear mixed models to the bimolecular rate constants k_i for each organophosphate separately with a random effect for the human subject, thus partitioning the variance into "between subject variance" or human variability, and "within subject variance" or experimental variability. From the latter two variances, Exponent derived the IntraClass Correlation (ICC), that is, the ratio of the human variability to the total variance. Even though Panel members considered the IntraClass Correlation the right metric to characterize human variability in response to organophosphate exposure, some Panel members remarked that due to the small sample size, the tests performed were underpowered.

As a second concern, one Panel member noted that the procedure used to derive coverage ratios for the bimolecular rate constants k_i, which relies on calculating upper percentile values in the distribution of the k_i's, was based on asymptotic considerations, all derived under the assumption of large sample sizes. Due to the extremely small sample size (n=4) used in the replicate analyses, the Panel recommended that alternative approaches be employed to derive percentiles of the distribution of the k_i's, such as, for example, the approach presented in Gilbert (1987). As done in reference to other charge questions, several Panel members highlighted the problem of incorrect uncertainty quantification in the replicate analyses: as in other statistical analyses, the bimolecular rate constants k_i are used in the replicate analyses as data and not as point estimates, as they truly are.

Finally, multiple Panel members found the interpretation of the results presented in Higgins et al. (2020) quite confusing due to contradictory conclusions reported in the document. Specifically, Panel members observed how in page 34 of the document, it was claimed that "[..] for omethoate and phosmet oxon, the ICC was small (values respectively of 20% and 3%), indicating large experimental variation relative to the total variability…." whereas, few lines later, the document states that "The large Naled ICC (value of 0.84) suggests that the experimental variability is a large contributor to the overall variability.". Various Panel members observed that both statements cannot be both simultaneously correct, and that the large Naled ICC suggested that the between individual variability is a large contributor to the overall variability.

Multiple Panel members also noted that the EPA Issue Paper "*Use of New Approach Methodologies to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment*" (US EPA, 2020a) has an incorrect statement in the paragraph just before Table 17 (page 75). The statement reads: "[..] Whereas, for phosmet oxon, only 3% of the total variability was due to differences in the 3 replicate analyses of the blood sample; 97% of the observed variability was due to the differences between human subjects." As the IntraClass Correlation for phosmet oxon was reported equal to 3%, Panel members believe that 97% of total variability was due to differences in the 3 replicate analyses.

A Panel member pinpointed the differences between organophosphates (OP) in terms of human variability. Although some of the differences between organophosphates can be ascribed to sampling and methodological variability more than actual human variability according to what was stated in Higgins et al. (2020), due to the extent of the differences between

organophosphates, the same Panel member recommended that organophosphates are considered on an individual-basis and not combined into a single, joint group.

In conclusion, in reviewing the complete set of results from the replicate analyses for 3 organophosphates, some Panel members noted that within human variability was indeed important for two out of the three chemicals examined pointing to the importance of estimating within sample/experimental variability. This point was also highlighted by more recent analyses performed by Exponent on additional organophosphates.

Reviewing the replicate data analyses discussed in Charge Question 8a, several Panel members observed that considering and characterizing both human and experimental variability are important for the estimation of intraspecies pharmacodynamic extrapolation factor (EF_{HD}). Thus, various Panel members expressed support for the generation of additional replicate data for other organophosphates. In designing these additional set of replicate data analyses, Panel members provided various suggestions. All Panel members recommended a larger sample size, with more human samples chosen so that their demographic characteristics are representative of the US general population. A Panel member recommended an approach to determine the needed sample size in situations, like the one encountered here, where no knowledge of the true underlying variability was available. The same Panel member recommended a two-stage approach, called "sample size re-estimation" where an initial, typically small sample is used in a first intermediary study, from which an estimate of variance was obtained. With knowledge of the variance, in the sample-size re-estimation approach, a final sample size was derived so to achieve the desired power. The Panel member observed that a two-stage sample size re-estimation approach could be used in this context, however the Panel member warned of the possibility of oversampling. At the same time, the Panel member noted that oversampling would be easily addressed in this situation.

Another Panel member recommended that future studies pay additional care and consideration to the chemical properties of the test substances, purity of the samples, as well as possible substance mobility on 96-well plates.

Two Panel members recommended that a more accurate accounting for uncertainty be carried out in additional replicate analyses. In particular, one Panel member recommended that the uncertainty associated with extrapolating responses occurring at a cellular level to responses occurring at the whole biological system level be correctly quantified, rather than ignored without providing any rationale for it. The same Panel member also observed that responses of full biological systems might be different between the very young and the elderly, as can be the case when considering neurological systems.

A Panel member recommended that the uncertainty in the bimolecular rate constant values, k_i be properly accounted for, by acknowledging the fact that the latter are estimates and not actual data values. The same Panel member recommended a multilevel modeling approach where the raw subject data on AChE phosphorylation rate for each human blood samples are used in the analysis rather than the point estimates.

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U.S. Department of Justice

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December 22, 2020

Via the Court's ECF filing system:

Honorable Molly C. Dwyer
Clerk of Court
United States Court of Appeals for the Ninth Circuit
The James R. Browning Courthouse
95 7th Street
San Francisco, CA 94103

Re: ***League of United Latin American Citizens et al. v. Andrew Wheeler et al., No. 19-71979 & No. 19-71932 (Consolidated)***

Dear Ms. Dwyer:

Pursuant to Federal Rule of Appellate Procedure 28(j) and Circuit Rule 28-6, Respondents wish to advise the Court as to post-argument developments regarding ongoing registration review of chlorpyrifos under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA").

On December 3, 2020, the Acting Director of EPA's Pesticide Reevaluation Division signed a Proposed Interim Decision for Reregistration for chlorpyrifos ("PID"). *See* 85 Fed. Reg. 78849 (Dec. 7, 2020). EPA is making the PID available for a 60-day public comment period.

In addition, a public, peer review meeting of the FIFRA Scientific Advisory Panel ("SAP") was held in September 2020, to consider new methodologies to evaluate the developmental neurotoxicity of organophosphate pesticides (the class of pesticides containing chlorpyrifos). *See* 85 Fed. Reg. 36580 (June 17, 2020). EPA anticipates that the PID may be revised in light of the SAP's recommendations.

Very truly yours,

Mark L. Walters
United States Department of Justice
Environmental Defense Section
Counsel for Respondents

cc: all counsel of record via the Court's ECF filing system

United States Department of Agriculture

March 7, 2021

Elissa Reaves, Ph.D., Director
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs, Environmental Protection Agency
1200 Pennsylvania Ave., N.W.
Washington, DC 20460-0001

Re: USDA Comments on the Proposed Interim Decision for Chlorpyrifos for Registration Review; EPA-HQ-OPP-2008-0850.

Dear Dr. Reaves:

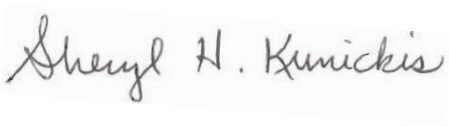
Thank you for the opportunity to comment on EPA's proposed interim decision for chlorpyrifos, which was posted on December 7, 2020 in the *Federal Register*. Chlorpyrifos is a non-systemic organophosphate insecticide, which acts by a neurotoxic mode-of-action, inhibiting acetylcholinesterase. It is classified by the Insecticide Resistance Action Committee (IRAC) as a Group 1B insecticide (IRAC, 2020). Chlorpyrifos is historically among the most widely used and critically important broad-spectrum insecticides in agriculture. Chlorpyrifos is registered on numerous agricultural crops and use sites, and for various application methods such as foliar sprays, tree trunk/vine drenches, soil applications (from pre-planting to post-emergence), seed treatments, spot treatments, and ear-tag treatments of livestock.

USDA appreciates EPA's broad understanding and consideration of the agricultural benefits of chlorpyrifos, as reflected in the Agency's recent updates to a previously published benefits analysis (USEPA, 2020a; USEPA, 2020b). While agricultural usage of chlorpyrifos has declined over time, there remain some critical needs for this insecticide, especially where effective alternatives are either unavailable or cost-prohibitive for growers. USDA compliments EPA's updated analysis of chlorpyrifos usage and benefits, which has helped to inform EPA's proposal and prioritization of critical needs. USDA has additional comments and concerns related to some of these identified high-use scenarios identified by EPA, as well as some scenarios not fully considered by EPA. In some cases, USDA contends that existing risk assessments are adequately protective to account for additional high benefit needs and that basic risk characterization may allow for retention of additional uses (vegetable seed, pecan, and sweet potato, for example) or some expansion of retained uses into additional states (tree fruits, for example). We also present additional information on uses where chlorpyrifos re-evaluation intersects with other concurrent registration review cases, along with additional stakeholder input on high-benefit uses for which EPA did/does not have available pesticide usage data. Some of these uses include mint, cranberries, sweet potatoes, sod farms, vegetable seed treatments, and vegetable/grass/forage seed production.

One of the most critical factors that will determine the extent to which EPA's proposal impacts growers is the Agency's decision on whether or not to impose a 10X FQPA safety factor. USDA has provided extensive comments to EPA on this question on previous occasions, and we urge EPA to ensure a rigorous and transparent review of the best available data to inform its final decision.

Our detailed comments are attached for your review. USDA stands ready to provide EPA with additional information on the benefits of chlorpyrifos, as well as additional characterization information to help address and/or refine EPA's risk assessment assumptions, if needed. Thank you again for your consideration, and please let me know if you would like to discuss this matter further.

Sincerely,



Sheryl H. Kunickis, Ph.D.
Director

FQPA Safety Factor

USDA has provided extensive comments on previous risk assessments for chlorpyrifos, and the benefits of its use in U.S. agriculture (USDA, 2017; USDA, 2016; USDA, 2015). While many of our concerns about EPA's decision to impose a 10X FPQA safety factor on all organophosphates (OPs) remain, we acknowledge the complexity of the current state of science addressing neurodevelopment effects. We further recognize that EPA has devoted tremendous resources to the continued study and evaluation of this issue, and support the Agency's commitment to a rigorous and transparent review of the best available data to inform its decision-making process for chlorpyrifos and other OP pesticides.

As part of its third revised human health risk assessment, EPA reviewed five recently-published open literature studies investigating the potential for developmental neurotoxicity following early life stage exposure to certain pesticides, including chlorpyrifos. While we welcome EPA's review of these additional studies, we request that EPA commit to a full systematic review of new studies that have been published since EPA's 2015 literature review. The Coalition of OP Registrants, for example, identified at least 40 new epidemiological investigations that have been published in the last five years (Smith, 2021a). We also ask that EPA ensure consistent application of its 2016 "Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides," particularly with regards to the analysis and reporting of study quality and the subsequent integration of these studies into weight of evidence analyses.

USDA further supports EPA's continued work on the new approach methodologies (NAMs) presented at the September 15-17, 2020 meeting of the FIFRA Scientific Advisory Panel (SAP). EPA's development of a battery of *in vitro* assays for evaluating developmental neurotoxicity (DNT) represent a significant step towards the longer-term objective of replacing the current *in vivo* DNT guideline study with a fit-for-purpose NAM battery that is less costly, less-reliant on animal testing, and more human-relevant. Using organophosphates as a case study for these efforts, EPA carried out *in vitro* to *in vivo* extrapolation using high-throughput toxicokinetic modeling to approximate NAM-derived administered equivalent doses (AEDs). These AEDs were compared to benchmark dose (BMD) and $BMDL_{10}$ values estimated from *in vivo* laboratory data on AChE inhibition in rats. In general, the comparisons demonstrated that NAM-derived AEDs for organophosphates are greater than or comparable to doses that inhibit AChE. For chlorpyrifos specifically, the NAMs did not identify an endpoint more sensitive than AChE inhibition. We appreciate EPA's incorporation of the scientific advice from the SAP—along with its consideration of additional *in vitro* assays for critical neurodevelopment processes that are being developed through international efforts—as part of the overall weight of evidence evaluation of the DNT potential for individual OPs, including chlorpyrifos.

Agricultural Benefits and Impacts of Proposed Mitigation

1X FQPA Safety Factor Proposal

If EPA does not ultimately impose a 10X FQPA safety factor to chlorpyrifos, USDA has minimal concern with the overall proposal to address risks under the presented 1X scenario, including revisions to personal protective equipment (PPE) requirements, modifications to re-

entry intervals, and regional restrictions on some uses. Any use-specific concerns under the 1X proposal will be discussed further below, by crop.

10X FQPA Safety Factor Proposal

For the proposal under the Agency's 10X safety factor retention scenario, USDA appreciates that EPA's preliminary drinking water exposure refinement allowed for the Agency's proposal to retain chlorpyrifos use (with some regional restrictions) for a number of high benefit uses, including alfalfa, apples, asparagus, cherries (tart), citrus, cotton, peaches, soybeans, strawberries, sugar beets, and wheat. For alfalfa, we appreciate that proposed retention of use in Washington, Oregon, Idaho, Montana, Colorado, and Wyoming includes areas where a substantial acreage of alfalfa is grown for seed, and where chlorpyrifos is an important tool for controlling *Lygus*. For asparagus, we agree with EPA's conclusion that benefits are most significant in Michigan—representing the most critical chlorpyrifos need for this crop—and we appreciate its proposed retention. Similarly, we agree with EPA's conclusion that observed usage and benefits on strawberries are most important to Oregon growers, for control of garden symphylans. However, a state-level ban proposed by Oregon may make impacts moot for this use. For citrus, we appreciate that usage is proposed to be retained in Florida and Texas, along with several other states in the deep South. With the state-level ban on chlorpyrifos proposed by California (CA), impacts from EPA prohibitions on CA citrus are rendered moot. This also applies to crops such as CA-grown seed alfalfa, CA-grown cotton, most tree nuts (except pecans), table grapes, plums/prunes, CA-grown strawberries, CA-grown Brassica vegetables, and CA-grown vegetable/grass/forage seeds.

For cotton, available agricultural market research data (AMRD) (2014-2019) indicate that stink bugs are a primary target pest for chlorpyrifos applications. USDA appreciates EPA's match of regional use retention to this need (i.e., the Southeastern United States) and we believe that overall negative impacts to cotton growers are likely to be minimal, so long as ground boom applications are not prohibited in the states where the use is retained. While the regional/state usage restrictions proposed on soybeans, sugar beets, and wheat may marginally impact some growers, we find that EPA's proposal reflects an earnest and reasonable effort to refine modeled surface water exposure in a way that minimizes overall impacts nationally. Retention of partial/regional access to chlorpyrifos will benefit a large proportion of producers for these crops, especially compared to full use cancellation scenarios.

USDA appreciates EPA's recognition of the importance of chlorpyrifos for public health uses, including mosquitoes, as well as the importance of OP active ingredients including chlorpyrifos for parasitic arthropod control in livestock agriculture. USDA received specific stakeholder feedback about the importance of darkling beetle applications in poultry houses (Owens, 2021), which appear to be slated for retention under both the 10X or 1X proposals. Chlorpyrifos also remains important for uses within USDA-APHIS programs targeting the Red Imported Fire Ant. EPA's usage and benefits analysis for non-crop uses (USEPA, 2020b) clearly articulated the associated benefits of chlorpyrifos for these use patterns and USDA has no additional comments or concerns at this time for these uses. We have confirmed that there are no additional APHIS programmatic needs for chlorpyrifos that have not already been discussed and acknowledged by EPA's PID and non-crop benefits assessment (USEPA, 2020b).

USDA notes however, particularly with regard to livestock uses, that a number of other OP active ingredients serve as chlorpyrifos alternatives and are also at various re-evaluation stages under registration review. Some of these alternatives include DDVP, naled, TCVP, coumaphos, diazinon, malathion, etc. We urge EPA risk managers to consider mitigation decisions on OPs strategically across these use patterns and to retain availability of at least one effective OP tool within each livestock use patter, to maintain viable resistance management flexibility. This is a key concern to prevent important animal and health protection efforts from becoming too dependent on other single modes-of-action that are commonly used, such as synthetic pyrethroids. USDA stands ready to offer input on how various active ingredients may be best prioritized across these important niche use patterns and stands ready to do additional stakeholder outreach and discussions on the most critical pest management needs for animal/livestock agriculture.

Specific Crop/Use Concerns Under the 10X Proposal

USDA has a number of larger remaining concerns for some specialty crop chlorpyrifos uses proposed for cancellation by EPA, either on a state-by-state or national basis. For some crops for which USDA largely agrees with EPA's benefit assessment conclusions, we wish to note some specific nuances and additional considerations around benefits. Other crops of concern represent uses for which EPA did not have any available usage data, such as cranberries, mint, sweet potatoes, sod farms, seed treatments, and forage/grass/vegetable seed production. These concerns are discussed in further detail below, by crop, and within the context of EPA's impact estimates, potential exposure refinements, and pest management benefits to growers. We will also discuss some concerns with EPA's proposed application restrictions that address occupational exposure.

Forage, Grass, and Vegetable Seed Production

As stated previously, USDA appreciates that EPA's proposal to allow continued chlorpyrifos use on alfalfa will address some critical needs of the alfalfa seed production sector. Given the relatively low acreage and highly localized nature of vegetable seed production in the Pacific Northwest (PNW), USDA requests that EPA also consider whether some further exposure/risk characterization for surface water might allow for continued use of chlorpyrifos on vegetable seed production, which is heavily concentrated in Washington, both in Northwestern Washington and also in areas of eastern Washington like the Columbia Basin (Walsh, 2021; Hartney, 2021).

Stakeholders have informed USDA that cabbage maggot control remains a critical issue of concern for hybrid cabbage and other Brassica seed producers in western Washington, including seed for cabbage, kale, collards, turnips, radishes, etc. Much of this acreage—approximately 200 acres grown in Skagit county, for example—is currently treated with chlorpyrifos for maggot control. Essentially all western Washington seed production is located in Skagit, Whatcom, and Snohomish counties, and all combined vegetable seed acreage in this region is less than 1,000 acres. This includes not only commercial seed production, but also industry stock seed that is important for breeding and variety development. This small area of Brassica seed production is crucial in supplying much of the world's Brassica seed supply (Hartney, 2021).

Because EPA has already proposed retention of chlorpyrifos on alfalfa in Washington—with alfalfa acreage totaling over 25,000 in these 3 counties alone (USDA, 2019)—we suggest that drinking water refinements conducted in support of alfalfa would be adequately protective of

vegetable seed production. USDA also reminds EPA that soil applications of chlorpyrifos are always incorporated at depths of 2-4 inches immediately after application out of necessity for efficacy. Crop consultants in this area have informed USDA, via stakeholders, that typical application rates for brassica treatments for cabbage maggots would be similar to conventional cole crop production, at 1 lb ai/acre for chlorpyrifos (Hartney, 2021). Other seed producers, such as growers of spinach and beet seed also use chlorpyrifos to control cornseed maggots and wireworms, with similar application methods and application rates. While cyantraniliprole and bifenthrin are available as alternatives for maggot control, stakeholders emphasized to USDA that retained access to chlorpyrifos is important for both resistance management (via either rotation or tank-mixing) and efficacy enhancement of these alternative products in at-plant soil applications (Hartney, 2021). Because less than 1,000 acres of vegetable seeds are grown in this 3 county region (as compared to ~25,000 acres of alfalfa, for which EPA is supporting retention of chlorpyrifos), USDA contends that the potential incremental increase in usage driven by vegetable seed uses would be well within the likely variability of alfalfa area grown and treated on a year-by-year basis. We also note that forages such as alfalfa are commonly part of existing crop rotations for many seed growers (Hartney, 2021). Practically speaking, this means some vegetable seed applications would literally be on the same fields where alfalfa is grown in other years.

In eastern Washington and the Columbia Basin, the main seed crops of concern are onions and carrots. Growers of these seed crops make foliar applications of chlorpyrifos pre-bloom (prior to placement of bees) for *Lygus* control (Walsh, 2021). For onions, chlorpyrifos is also effective against onion maggots when applied to soil at planting, similar to what was described previously for hybrid cabbage, and as would be done for commercial bulb onion production as a crop. As with western Washington, USDA suggests that EPA's existing drinking water exposure refinement for alfalfa would again be adequately protective of drinking water exposure to chlorpyrifos from these vegetable seed uses, based on the same rationale around existing alfalfa acreage. Stakeholders have informed USDA that almost all seed crop acreage in eastern Washington is located in Adams, Franklin, Kittitas, and Walla Walla Counties. Seed crops such as sweet corn, beans, peas, sugar beets, canola, onions, and carrots all combine for only about 10,000 total acres grown in this region (Walsh, 2021). This estimate is upper-bound with regard to likely chlorpyrifos usage, since seed sweet corn is not a high benefit scenario and this accounts for a large portion of this total acreage. By comparison, alfalfa forage production in these 4 counties totals over 90,000 acres and this is in addition to 10,000 acres of seed alfalfa grown for seed in Walla Walla County. This yields a total of ~100,000 total alfalfa acres grown (USDA, 2019) for which EPA has assessed safe use of chlorpyrifos in eastern Washington. As with the western Washington scenario discussed previously, we contend that the incremental inclusion of vegetable seed acreage within this footprint of alfalfa (which would also vary somewhat year to year) already assessed for chlorpyrifos surface water exposure should not change EPA's drinking water assessment outcome. We strongly urge EPA to consider retaining chlorpyrifos use on vegetable seeds in all of Washington, as the use provides substantial benefits to a critically important but spatially small agricultural sector. We believe that additional characterization to existing exposure assessments could be done without necessitating a new risk assessment for any of these seed production uses.

Similar to Washington, Oregon also has a significant seed production sector, which beyond vegetables (in the Willamette Valley and Columbia Basin), includes clover seed and grass seed

production (Rondon, 2021; Kaur, 2021; Lightle, 2021). While the benefits of chlorpyrifos are significant for these crops, Oregon's proposed state level ban may render the availability of chlorpyrifos moot for these growers. However, there is a remaining possibility that granular applications of chlorpyrifos may be retained by Oregon, which could potentially still allow for applications of granules at planting for grass and clover seed producers, which bury and incorporate seed at approximately ¼" below the soil surface. We suggest that similar to alfalfa seed, potentially allowing continued use of chlorpyrifos at planting would be beneficial for clover and grass seed growers throughout Oregon and Washington (Lightle, 2021; Walsh, 2021). USDA is happy to engage further with EPA and stakeholders to develop additional use specific information that would assist EPA with characterization.

Non-Citrus Tree Fruit Trunk Drench Applications—Including Fruit Nursery Production

We appreciate EPA's thoughtful analysis and consideration of the importance of borer pests on apples and stone fruit production (USEPA, 2020a). Growers have sporadic but critical needs to control these pests, since damage can impact the lifetime productivity of orchards. We agree with EPA's conclusions on the critical importance of chlorpyrifos trunk sprays to manage borer pests, including both clearwing moth species (e.g., Dogwood borers on apple, Peachtree/Lesser peachtree borers on peaches, and other borer species on plums and cherries) and Ambrosia beetles (on apples only). We agree with EPA's impact estimates concluding that mating disruption options are considerably more costly on a per acre basis, especially noting the labor costs for hand-application of pheromone dispensers in pome and stone fruit orchards. While mating disruption products offer reasonable efficacy that can be adequate in some regions, numerous stakeholders have informed USDA and EPA that this efficacy is not consistent enough to provide a reliable one-for-one replacement option for chlorpyrifos trunk treatments, and we appreciate EPA's recognition of this specific prior feedback in their benefits assessment (USEPA, 2020a).

As a specific sub-sector of tree fruit production, USDA is also concerned that tree nursery producers have a particularly acute need to retain chlorpyrifos, given the high levels of borer pest pressure that commonly exist in high density nursery stock propagation. While overall acreage of this production is small, the need for borer control is critical, both for phytosanitary purposes (to prevent selling infested trees) and protection of young tree structure and quality. Two large tree fruit nursery producers in the eastern United States have indicated to USDA that mating disruption is simply not adequate to manage this level of pest pressure, making chlorpyrifos applications indispensable for their needs (Anonymous, 2021a; Anonymous, 2021b). Unlike production orchard applications that sometimes require use of pressurized hand guns, both nursery producers confirmed that more conventional ground-boom applications were adequate for their needs. In both cases, modified boom sprayers (sometimes with drop nozzles) are used in treating nursery stock blocks with large droplets that are not prone to drift. These practices are typical for most other large tree fruit nursery producers in the United States, and it was noted that other nursery operations could use modified airblast applications for trunk targeted applications.

Because trunk drench applications are a critical, but ultimately sporadic need for orchard crop production (Epstein, 2021), we contend that EPA's drinking water exposure assessment for apples, peaches, plums, and cherries—used mainly in support of retained airblast uses for these crops—would highly over-estimate the likely surface water exposure from trunk sprays. Because trunk drenches are designed to allow both bark uptake and soil penetration at the base of the

trunk (especially for stone fruits planted at lower tree density), widespread orchard floor surface deposition does not occur. Further, because applications targeting borers are sporadic, because the application parameters are not conducive to drift, and because the overall percent crop treated (PCT) for this use pattern is far smaller than airblast uses on a year-by-year basis (AMRD, 2015-2019), USDA suggests that EPA could likely retain access nationally to the trunk-directed use pattern, even if regional restrictions are needed for airblast applications. We further suggest that if EPA were to propose restrictions against applying before large storm events are forecast, or restrictions against applications to water saturated soils, for example, it could help to further assure a limited opportunity for runoff under most real-world conditions. Such label restrictions would not negatively impact growers.

If such characterization is plausible, USDA urges EPA to allow chlorpyrifos trunk drench applications nationally. This would be highly beneficial to both orchard and tree fruit nursery producers, even if dormant/delayed-dormant airblast applications remain restricted by state. Stakeholders from minor peach production states (for example, Mississippi) have indicated that borers are a huge problem for their relatively small commercial production acreage (Layton, 2021). USDA contends that peach tree borers especially are a highly problematic pest for which no adequate chlorpyrifos alternatives exist—particularly in the Southern United States, where pest pressure is high and hot temperatures lead to multiple generations of borers attacking orchards. In many of these smaller acreage production systems, we suggest to EPA that trunk drenches are a more proximate pest management need.

A consortium of tree fruit IPM experts have further indicated to USDA that retaining pressurized hand gun applications is critically important for these trunk drench applications (Wise, 2021; Walgenbach, 2021; Butler, 2021; Polk, 2021; Nielsen, 2021; Jentsch, 2021; Agnello, 2021). USDA agrees that handgun applications are a critical need for producers of most tree fruits, especially stone fruits like peaches, cherries, and plums (grown outside of California). While modified boom sprayers have been developed for trunk targeting applications, their development has been challening and costs for growers are significant. Especially for tart cherries (Wise, 2021) and peaches (Walgenbach, 2021; Nielsen, 2021; Polk, 2021), thorough coverage of trunks is necessary for efficacy against peachtree borers and lesser peachtree borers. Many times, this can only be accomplished with hand gun drenches that can be manually directed to deliver maximal coverage of the burr-knot (for apples), tree trunk, and soil-trunk junction (for stone fruits).

USDA also fully agrees with EPA's conclusion (USEPA, 2020a) that mating disruption alternatives are not adequate alternative options for many of the national peach/nectarine production areas of the United States, particularly Georgia and the deep South. Unmitigated outbreaks of borer pests on tree fruits pose a significant threat to profitability as they can cause tree death and reduce overall per acre productivity. USDA acknowledges the occupational risk concerns surrounding the use of pressurized handgun applications and is willing to engage further with EPA regarding the high benefits of this use and discuss alternative mitigation options that could partially address EPA's concerns while retaining practical use of this application method for growers.

Apples and Pears

USDA appreciates EPA's recognition of the importance of chlorpyrifos for apple producers, both for delayed dormant airblast applications and trunk drench applications targeting borers (see Tree Fruit Trunk Drench Applications section). We agree with EPA's conclusions that early season dormant or delayed dormant chlorpyrifos applications remain an important part of season-long IPM control programs for pests such as rosy apple aphids and San Jose scale. We have no concerns with the proposed requirements for engineering controls and PPE modifications for airblast applications. We appreciate EPA's efforts to refine surface water exposure and support the proposed allowances for continued use in a number of apple producing states. However, USDA and associated stakeholders (Walgenbach, 2021) are very concerned with North Carolina being left out of this group, especially given that chlorpyrifos use on peaches and nectarines is still proposed to be retained in this state. Based on the most recent available census data (USDA, 2019), nearly 75% of North Carolina apple acreage is located in Henderson County. USDA suggests that some additional marginal refinement with localized percent cropped area (PCA) and PCT data may allow for continued access to chlorpyrifos for NC apple growers. Similarly, we note that the majority of apple production in Utah is located in Utah County, near Provo. Significant apple acreage is also grown in the New England states, Minnesota, and Wisconsin. USDA appreciates that chlorpyrifos us will still be retained for a large proportion of national apple production.

USDA agrees with EPA's analysis and conclusion of low relative chlorpyrifos benefits for pears (to control scale at delayed-dormant timing). However, we do note that drinking water refinements in support of retention of apples may potentially also be protective of pears if the same crop data layer (orchards) was used, and if pear-specific PCT data are considered. We request EPA consider if retention of early-season use on pears (especially in Washington) might be possible via such refinement/characterization, without the need for a revised risk assessment.

Cherries (Sweet)

While USDA acknowledges that overall usage of chlorpyrifos has declined on sweet cherries (USEPA, 2020a; AMRD, 2014-2019), there is an important niche benefit that remains for sweet cherries grown in Washington. Because apple and grape mealybugs transmit little cherry virus, the continued availability of chlorpyrifos is very important to growers targeting this vector pest. Washington State University guidelines recommend use of chlorpyrifos at delayed dormant timing (both on cherries and on apples grown near cherries) to control overwintering mealybug females (WSU, 2020). While chlorpyrifos alone is not an adequate tool to manage mealybugs, the control of over-wintering females with chlorpyrifos is an important component of a season-long program.

Available AMRD provide additional evidence for the importance of this use. While overall chlorpyrifos treated acreage has generally declined on cherries in Washington in recent years, the proportion of the reported usage that targets mealybugs has *increased* and now represents the vast majority of reported chlorpyrifos usage in the most recent years (AMRD, 2014-2019). USDA suggests that if EPA's refinement for Pacific Northwest (PNW) apples (presumably based on the orchard data layer for PCA analysis) resulted in modeled surface water exposure below the drinking water level of concern (DWLOC), this finding may be adequately protective for Washington sweet cherries, especially when also considering the low overall state-level PCT. Retention of chlorpyrifos for sweet cherry use in Washington would allow established management programs for mealybugs to continue (on both apples and cherries) and reduce

negative impacts to tree fruit producers from little cherry virus. As with apples, we have no concerns with the proposed requirements for engineering controls and PPE modifications for airblast applications.

Cherries (Tart)

USDA appreciates EPA's proposal to retain use of chlorpyrifos for tart cherries grown in Michigan under the 10X scenario proposal, which represents the vast majority of tart cherry production in the United States. We have previously commented on the critical need for retaining trunk drench applications with pressurized hand guns (see Tree Fruit Trunk Drench Applications section). However, we note that county-level census data (USDA, 2019) suggest that additional marginal refinement/characterization of potential surface water exposure might also allow for tart cherry growers in Wisconsin, Utah, Washington, and Pennsylvania to retain access without exceeding EPA's DWLOC, for both airblast and trunk drench uses. This allowance would further minimize negative grower impacts nationally (Harris, 2021).

We note that for production in Wisconsin (approximately 2,000 acres), essentially all tart cherries are grown in Door County, on the eastern peninsula extending into Lake Michigan. General soil and weather characteristics and production practices in this county are likely to closely match the main cherry producing areas of Western Michigan. USDA suggests that surrogate use of PCT estimates from Michigan, when combined with PCA estimates for this single county, may allow for retention of chlorpyrifos use. Utah is also a significant production area for tart cherries, with approximately 5,000 acres grown, almost all in Utah County (near Provo). Similarly, we note that the vast majority of tart cherry production in Washington is located in only three counties (Franklin, Grant, and Walla Walla) and a large portion of Pennsylvania production is in one county (Adams). While New York is still a major tart cherry producing state, the state-level ban of chlorpyrifos makes federal availability moot for that state. We have no concerns with the proposed requirements for engineering controls and PPE modifications for airblast applications.

Peaches and Nectarines

USDA appreciates EPA's analysis of chlorpyrifos benefits for peaches and nectarines and we agree with their conclusions around the need for dormant/delayed dormant applications to target scale pests, etc. We have previously commented on the critical need for retaining trunk drench applications with pressurized hand guns (see Tree Fruit Trunk Drench Applications section). Stakeholders have confirmed to EPA that the dormant/delayed dormant airblast use remains a critical need for peach producers (Krawczyk, 2021). Much like the discussion for cherries, USDA is concerned that drinking water refinement may have left out significant areas of peach production, including Mississippi (left out, while Alabama was included), Utah, Colorado, and New England states. These concerns are also relevant under EPA's 1X scenario proposal. Ultimately, USDA appreciates that chlorpyrifos will still be retained for a large proportion of national peach and nectarine production acreage outside of California (USDA, 2019). Similar to our prior comments on other tree fruits, we have no concerns with requirements for engineering controls and PPE modifications for airblast applications.

Pecans

USDA appreciates that EPA's analysis of likely impacts for the loss of chlorpyrifos in pecans accounts for control of aphids, phylloxera, and pecan nut casebearer. While we have no specific disagreements with EPA's conclusions on alternatives and cost impacts, we are concerned that EPA's proposal to cancel pecans may not have accounted for substantial drinking water exposure refinements that were already used to support peaches and nectarines in many of the same states where pecans are most commonly grown and where this acreage would potentially be already accounted for in EPA's drinking water assessment. Based on using the orchard crop data layer for refinement of PCA, and the ability to further refine exposure estimates with pecan PCT (approximately 10-20% according to EPA's analysis and based on more recent usage data), USDA suggests existing risk assessments for peaches may be adequately protective for pecan use. We urge EPA risk managers to consider whether chlorpyrifos usage in states such as Georgia and Texas can be retained based on the retained peach/nectarine uses. Because Georgia and Texas also represent two of the higher usage scenarios for pecans, such an allowance would eliminate a large majority of the projected chlorpyrifos cancellation impacts for pecan growers on a national basis. Similar to our prior comments for tree fruits, we would have no concerns with requirements for engineering controls and PPE modifications for airblast applications.

Sweet Potatoes

EPA's analysis of benefits did not include any detailed discussion of sweet potatoes. Because chlorpyrifos must be incorporated into soil at 4-6 inches to be effective, USDA suggests that preliminary estimates for drinking water exposure might potentially be estimated, characterized, or bounded in a way that allows for sweet potato use pre-planting to remain viable, without necessitating an entirely new risk assessment. We note that many chlorpyrifos product labels already have a specific requirement for immediate incorporation after application and we suggest this could be uniformly applied across other labels. We further suggest that if EPA were to propose restrictions against applying before large storm events are forecast, or restrictions against applications to water saturated soils, for example, it could help to further assure a limited opportunity for runoff under most real-world conditions and address EPA's modeled surface water exposure concerns.

Chlorpyrifos remains an important management tool for control of wireworms and flea beetles on sweet potatoes prior to planting, via tillage-incorporated applications. IPM experts report to USDA that usage of chlorpyrifos is still significant in sweet potatoes. An estimated 50% of acreage is treated in NC, which is the leading sweet potato production state in the United States. (Huseth, 2021; USDA, 2019). For Mississippi and Louisiana, a range of approximately 60% to 80% of acreage is estimated to be treated (Musser, 2021; Smith, 2021b). Because California has already banned the use of chlorpyrifos, impacts from EPA's proposals are moot for those growers. USDA is primarily concerned that EPA's proposal would cancel sweet potato use altogether under a 10X safety factor scenario. EPA's proposal would also prohibit aerial applications to sweet potatoes. For the proposed additional PPE requirements and engineering controls associated ground-boom applications to sweet potatoes, stakeholders have informed USDA that these restrictions would not negatively impact many growers, so long as chlorpyrifos remains available for use.

Due to high efficacy, long persistence, and low cost, chlorpyrifos is a highly effective soil-applied insecticide, along with alternatives such as bifenthrin, imidacloprid, and clothianidin. Chlorpyrifos is often rotated and sometimes tank-mixed with these alternative products for pre-

plant applications to manage resistance and enhance efficacy. Chlorpyrifos provides a substantial resistance management benefit for growers, as an organophosphate registered for pre-plant use to target soil insects such as wireworms, flea beetles, and cucumber beetles. Ethoprop is also registered for pre-plant use on sweet potatoes, with a similarly long pre-harvest interval. IPM experts have suggested that in the absence of chlorpyrifos, the soil use of bifenthrin, imidacloprid, or clothianidin alone at pre-planting may put additional resistance selection pressure on the overall IPM program for sweet potatoes. Chlorpyrifos helps to modulate this selection pressure as a distinct mode-of-action. Finally, USDA notes that the neonicotinoid active ingredients imidacloprid and clothianidin and the organophosphate ethoprop are also undergoing concurrent registration review, with application rate reductions already proposed in the neonicotinoid PIDs. We urge EPA risk managers to strategically consider the interacting impacts of these proposals, since the loss of chlorpyrifos would add considerably to the benefits profile of pre-plant use of neonicotinoids and ethoprop, and vice-versa.

Vegetable Seed Treatments

We appreciate that EPA has proposed retaining a number of vegetable seed treatments under the 10X scenario with regard to potential dietary exposure, but note that some occupational concerns drive use prohibitions that may negatively impact producers, especially for crops such as beans and peas. Stakeholders identified the bean and pea seed treatments as having particularly high benefits for growers, due to their effectiveness against seedcorn maggots (Owens, 2021), which are very difficult to scout. Particularly for peas and beans grown in the mid-Atlantic region, March to mid-April planting times overlap greatly with the flights of overwintering flies that lay eggs into soil, making this an especially vulnerable planting period (Owens, 2021). While Brassicas are also of some regional concern, USDA urges EPA to account for the significant grower benefits of seed treatments on peas and beans and consider retaining access to this important IPM option.

Crops Where Loss of Chlorpyrifos Will Impact Other Registration Review Analyses

Cranberries

USDA appreciates EPA's analysis of chlorpyrifos benefits for cranberry producers. While alternatives exist for most target pests, chlorpyrifos does represent a reliable broad-spectrum 'rescue' option for many producers, and we agree with EPA's overall assessment of impacts. While cranberries were not identified as a critical need crop by EPA or registrants, we suggest that the overall usage profile cited by EPA indicates that benefits are significant. If possible, we urge EPA to consider whether existing assessments might be characterized for drinking water exposure from cranberries without necessitating a new assessment. For example, chlorpyrifos assessments for tree fruit uses in New Jersey, the upper Midwest, and the PNW may be adequately protective of potential water exposure from use on cranberries. We also urge EPA risk managers to strategically consider that one primary chlorpyrifos alternative, diazinon, is also being re-evaluated concurrently under registration review. Loss of chlorpyrifos could significantly affect the relative benefits profile for diazinon and vice-versa.

Mint

Chlorpyrifos remains an important insecticide for mint growers for control of mint root borers, cutworms, and armyworms. Chlorpyrifos applications also provide some incidental control of aphids, flea beetles, craneflies, and wireworms, even though these are not primary target pests in most situations. Based on a 2012 industry-initiated survey, approximately 30-35% of mint acreage is treated nationally on average with chlorpyrifos and it was reported as the third most widely-used insecticide. This general usage characterization remains similar today (Salisbury, 2021). While ethoprop is also registered for soil application to mint, its use is limited to applications either at-planting or post-harvest only, whereas chlorpyrifos has the benefit of application flexibility within the growing season. Acephate is another OP option for late-season rescue treatments that has significant benefits for growers.

While we agree with EPA's characterization of potential substitution options, stakeholders have informed USDA that fumigation is generally cost-prohibitive to most mint producers and that for mint root borers, chlorpyrifos is generally regarded as having superior efficacy to diamides (Salisbury, 2021). However, the main benefit of chlorpyrifos for mint producers, particularly relative to the alternative ethoprop, is application flexibility. Because ethoprop can only be applied at planting or post-harvest, it is not viable as an in-season intervention, which can be important when rescue treatments are needed. Further, for double-cut mint (typically done in spearmint and sometimes done in peppermint, depending on the irrigation scenario), the ability to make two applications in the same season makes chlorpyrifos a very cost-effective broad-spectrum option for many growers (Salisbury, 2021). Especially in Washington, post-cutting applications represent a key application point where chlorpyrifos benefits are high. USDA urges EPA risk managers to consider that losing chlorpyrifos would significantly enhance the already high benefits profile of ethoprop, given its pre-plant and post-harvest utility against wireworms, symphylans, and nematodes, and also for acephate, which is a more directly comparable chlorpyrifos alternative for late season rescue treatments. The loss of ethoprop or acephate could similarly increase the benefits profile of chlorpyrifos.

Peanuts

While USDA generally agrees with EPA's conclusions of low per acre benefits of chlorpyrifos for peanuts, we note that the market-leading soil insecticides for peanuts—phorate and imidacloprid—are also both under concurrent re-evaluation for registration review. Phorate is a systemic organophosphate that confers important efficacy against thrips as well as soil-dwelling pests when used at planting. Phorate also has direct efficacy on both vectors and plant-induced defenses that act directly on tomato spotted wilt virus on peanuts (Cabrara, 2020). USDA has previously commented on the ecological risk assessment posted for phorate regarding this unique efficacy benefit. While chlorpyrifos is non-systemic and not effective against thrips, it does have efficacy against wireworms and other soil-dwelling species that can be controlled by phorate. If phorate or imidacloprid uses are cancelled on peanuts, we would expect the benefits profile of chlorpyrifos to increase substantially. We urge EPA risk managers to consider the interacting impacts of these parallel cases, since the loss of chlorpyrifos would add to the relative importance of phorate and imidacloprid and vice-versa.

Sod Farms

USDA received mixed stakeholder feedback regarding the use of chlorpyrifos on sod farms. We appreciate EPA's recognition of chlorpyrifos as a market leading material for turf/sod farm users

based on 2011 usage data (USEPA, 2020b). Chlorpyrifos still has some significant benefits for sod producers, most notably the effective 'curative' treatment for soil pests such as grubs that have grown to advanced late-instar larval stages and are thus more difficult to control than younger stages. A southern respondent (Dale, 2021), indicated that grubs tend to be a more problematic issue in northern states, since Florida's sod production is on a shorter growth and harvest interval than more temperate zones. While the loss of chlorpyrifos could pose inconveniences for some producers, it is not widely considered to be as integral of a pest management tool today as it was a decade ago, as more varied alternatives are available for many target pests. Another respondent indicated that chlorpyrifos was no longer listed as part of published sod farm recommendations for the state of Mississippi, (Layton, 2021). This tends to support the conclusion that chlorpyrifos benefits have decreased in recent years for most sod growers. USDA notes that EPA's decision on chlorpyrifos could interact with previously assessed benefits for neonicotinoid active ingredients used as primary grub control tools on turf, as these active ingredients are still under concurrent re-evaluation for registration review.

Other Occupational Risks, Aerial Applications, and Drift Management

Occupational Risks

As mentioned previously, USDA has no concerns with adding engineering controls and PPE requirements for airblast applications to tree fruits. We have already commented extensively on the need for pressurized hand gun applications for trunk drench applications on tree fruit and the high benefits associated with that application method. We support the proposed additional protections proposed for applications with ground boom sprayers and note that any cancellations of ground-boom application methods would result in *de facto* use cancellations. USDA urges EPA to retain seed treatment uses for vegetables based on high benefits discussed previously, especially for beans and peas. USDA has no concerns with prohibitions on backpack sprayer applications, so long as low-pressure handwand use remains available, especially for livestock premises, spot treatments, poultry house treatments, and APHIS programmatic needs for red imported fire ants. We have no concerns with EPA banning the use of human flagging, as this practice is no longer relevant in agriculture.

For post-application occupational exposure risks, USDA generally has few concerns with EPA's proposed changes to re-entry intervals (REIs). We note that a 5 day REI for cranberries is likely to be highly burdensome to growers. But if this use is not retained under the 10X FQPA safety factor proposal, that impact is moot. For tree fruits, USDA has no major concerns with proposed REIs, but we note that orchard activities are minimal (e.g., no hand-thinning or any plausible foliar contact) at dormant and delayed-dormant timing. Further, for trunk drench applications, we contend that potential worker exposure to residues is negligible since these are specifically directed away from foliage and fruit.

Aerial Application Restrictions

USDA is concerned that EPA's proposed cancellation of aerial applications of chlorpyrifos will negatively impact growers who need to utilize aerial applications in exigent circumstances. This can occur when weather (i.e., fields that are too wet) or other rapid pest outbreak conditions preclude the practicality of ground applications, particularly for large acreage crops. This concern is shared by the National Agricultural Aviation Association (NAAA) as communicated

to USDA (Bretthauer, 2021). We note that EPA's use and usage summary shows that significant proportions of treated acreage are made by air for high benefit crops, including soybeans, wheat, and alfalfa. Sweet corn is also very commonly treated via aerial application.

While USDA agrees with EPA's characterization around the relative infrequency of aerial applications for many of the assessed high-benefit specialty crops uses, we suggest that the flexibility to retain this application option is still a major benefit to growers. Availability of aerial application provides growers with a rapid-response option that is crucial when needed to respond to pest outbreaks, even if that need is infrequent or sporadic. Further, USDA contends that the occupational risks associated with aerial chlorpyrifos use may not have been fully characterized relative to these benefits, given the way EPA's potential use of a 10X FQPA safety factor appears to be applied across all populations, despite the endpoint of concern not being specifically associated with adult exposure. Because neither bystander nor occupational drift drive any risks of concern, these estimates alone do not appear to support EPA's proposed ban on aerial uses.

USDA suggests to EPA that other options exist to address uncertainties around occupational exposure to chlorpyrifos for aerial uses. For example, we note that aerial applicators and growers would not be negatively impacted were EPA to require closed mixing/loading systems and/or limit aerial applications to liquid/flowable formulations only. This would further reduce the potential for problematic occupational exposure, while retaining key pest management flexibility for growers. USDA received direct input from NAAA to this effect (Bretthauer, 2021), indicating that they would support such restrictions on aerial applications of chlorpyrifos. USDA fully supports the proposals submitted to EPA from the NAAA regarding wind speed, boom length, and associated restrictions applicable to aerial applications.

Drift Management

USDA appreciates EPA's assessment of drift and agrees that there are no concerns for bystander drift exposure under either a 10X or 1X scenario. Given this lack of risk concerns, we request that EPA risk managers consider adoption of more standardized and consistent drift mitigation language that reflects commonality with other recently completed interim decisions, including an increase in the wind speed limitation to 15 mph and requiring applicators to use nozzles and pressure settings that will deliver medium or coarser droplet sizes for both aerial and ground applications. Allowing this flexibility would benefit applicators needing to make applications in areas of the country with challenging weather conditions. Importantly, the added consistency with many other product labels will reduce the likelihood of a problematic situation where restrictions on entire tank mixes might be driven by chlorpyrifos as the most restrictive labeled product in an application.

In addition to supporting the suggested verbiage offered to EPA by NAAA, discussed above, USDA requests that EPA consider adopting the following language on droplet sizes that has been consistently approved and/or proposed more recently for numerous other PIDs and IDs under registration review. This language would be for both ground-boom and aerial applications:

> *"Applicators are required to select nozzles and pressure that deliver medium or coarser droplets as indicated in manufacturers' catalogues and in accordance with American Society of Agricultural & Biological Engineers Standard 572.1 (ASABE §572.1)."*

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October 15, 2021

By Electronic Mail

U.S. Environmental Protection Agency
Federal eRulemaking Portal (http://www.regulations.gov)
Office of Administrative Law Judges (OALJ) E-Filing System (https://www.epa.gov)

RE: Objections, Request For Stay, Request For Guidance -- EPA-HQ-OPP-2021-0523

To Whom It May Concern:

CropLife America (CLA) and RISE (Responsible Industry for a Sound Environment) submit these objections to EPA's August 30, 2021 decision to revoke all chlorpyrifos tolerances under Section 408 of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a.[1] CLA and RISE request a stay of the effective date of this decision to permit time to address the concerns discussed here without harming the interests of our members and other stakeholders. To help provide greater clarity for our members and other interested members of the public, CLA and RISE also request that EPA develop and publish guidance on how it will implement its regulations at 40 CFR 180.32(b) concerning what constitutes "reasonable grounds" for a petition seeking to modify or revoke a tolerance or exemption from tolerance.

CLA is a non-profit trade association representing companies that develop, register, and sell pesticide products in the United States. CLA represents the 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's member companies produce most of the crop protection and pest management products regulated by EPA under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. Section 136, et seq., and Section 408 of the FFDCA.

RISE is a national trade association representing manufacturers, formulators, distributors, and other industry leaders involved with specialty pesticides and fertilizers used by professionals and consumers. RISE promotes the safe and responsible use of pesticides to control pests and invasive species that are detrimental to our health and our environment.

EPA's decision adversely impacts CLA and RISE members who hold chlorpyrifos registrations by imposing an unnecessarily broad revocation of chlorpyrifos tolerances rather than a more appropriate tailored approach. The revocation also fails to provide sufficient time to adjust practices and lacks the guidance that growers, applicators and others in the supply chain need in order to comply when the tolerance revocations go into effect at the end of February 2022. In addition, EPA is vague on the manner in which its registration review under FIFRA will

[1] Chlorpyrifos; Tolerance Revocations, Final Rule, 86 Fed. Reg. 48315 (August 30, 2021).

integrate with the tolerance revocation. CLA and RISE request that EPA stay the effective date of its decision to address these issues and others raised in the following seven sections.

A. EPA Improperly Revoked Tolerances For The Eleven Crops That It Found Met The Safety Standard In Its 2020 Proposed Interim Decision

EPA relies on the Ninth Circuit decision, *League of United Latin Am. Citizens v. Regan*, 996 F.3d 673 (9th Cir. 2021) (*LULAC*), to justify its decision to revoke all food tolerances for chlorpyrifos without distinguishing among the variety of different food commodities affected by the Agency's decision. The Ninth Circuit did not mandate that EPA revoke all tolerances. It allowed the Agency to revise tolerances based on existing information. The Court provided EPA with options, stating that:

> such a final regulation could take one of two forms: either it could [1] revoke all chlorpyrifos tolerances or [2] it could modify chlorpyrifos tolerances *and* conclude that under the new tolerances there is a "reasonable certainty that no harm will result" due to "aggregate exposure to the pesticide chemical residue" that would result from such modified tolerances, including "to infants and children."[2]

The Ninth Circuit made clear that EPA could "modify chlorpyrifos tolerances, rather than [] revoke them," provided the decision included the required safety determination.[3]

EPA's record contains sufficient information to determine that at least some tolerances and uses satisfy the safety standard and should not be revoked. For example, EPA's December 2020 Proposed Interim Registration Review Decision (PID) identified eleven crops that met the safety standard and did not pose a risk from food residues or drinking water concentrations.[4] Chlorpyrifos tolerances apply to over eighty distinct food commodities and range from 0.01 parts per million (ppm) for apples to as high as 20 ppm for citrus oil. Each needs to be evaluated on its own merits.[5]

In the PID, EPA identified eleven commodities that could retain high-benefit agricultural uses in select regions, considering dietary exposure and impacts of drinking water on infants, children, and women of reproductive age. EPA made carefully considered and well researched findings to determine that these commodities would not pose potential risks of concern using the default 10X Food Quality Protection Act (FQPA) safety factor.[6]

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[2] *League of United Latin Am. Citizens v. Regan*, 996 F.3d 673, 702 (9th Cir. 2021).
[3] *Id.*
[4] U.S. Environmental Protection Agency. December 3, 2020. Chlorpyrifos Proposed Interim Registration Review Decision Case Number 0100, EPA-HQ-OPP-2008-0850-097 (PID) at 40.
[5] *See* 40 C.F.R. § 180.342(a).
[6] PID at 19, 40.

EPA's revocation decision is internally inconsistent; it acknowledges the PID's safety finding with respect to these uses but nonetheless revokes them.[7] EPA did not revisit or reassess the PID safety finding for the eleven uses. Instead, the Agency suggests that it is bound to assess the aggregate exposure from all "currently registered" uses.[8] Nothing in the Ninth Circuit decision or the regulatory process requires that result. EPA can reconfirm its safety finding for these uses, can modify the tolerances if needed, and can undertake appropriate actions under FIFRA to allow registrations and labels to continue for certain food uses that meet the safety standard (as is planned for non-food uses).

EPA's chosen approach creates a procedural dilemma. Having delayed its decision regarding which chlorpyrifos registrations should be cancelled, EPA asserts it must consider aggregate exposure to *all* registered uses and must now revoke all tolerances. Moreover, when the Agency does address cancellation, there will be no basis to retain registrations as the corresponding tolerances have been cancelled. This approach to revoking all tolerances lacks scientific and legal justification. Instead, the Agency should either confirm or reassess its determination whether a subset of "highly beneficial" uses and tolerances satisfy the safety standard. At a minimum, EPA should differentiate the eleven crops that it concluded met the safety standard in the PID, finalize a safety determination for those crops and retain their tolerances, and take appropriate action under FIFRA to allow these limited uses to continue.

B. EPA Should Revise Its Rule And Retain Import Tolerances As Needed For Commodities That Do Not Pose A Dietary Risk

EPA's rule broadly revokes all tolerances for domestic and imported commodities, without distinguishing exposures from imported versus domestic commodities and without considering whether import tolerances are appropriate for certain commodities. Retaining certain chlorpyrifos tolerances as import tolerances is supported by EPA's guidance, by legal precedent, and by EPA's risk determinations in the August 2021 decision. The Agency should provide a process for the request, consideration, and approval of chlorpyrifos import tolerances.

EPA's guidance states that "as domestic uses are canceled during the pesticide reregistration process, or for any other reason (other than dietary risk), EPA will consider requests for modifying or maintaining the corresponding tolerance to allow the continued import of treated food into the U.S." provided EPA can make the required "safety finding."[9] The guidance explains that:

> Registered pesticide uses may be canceled for a variety of reasons including internal business reasons, dietary risk concerns, or non-dietary risk concerns. In many cases, a tolerance is no longer needed after a registered use in this country is canceled, and EPA routinely proposes to revoke such tolerances. However, use in other countries may

[7] 86 Fed. Reg. at 48333.
[8] *Id.*
[9] Pesticides; Guidance on Pesticide Import Tolerances and Residue Data for Imported Food; Request for Comment, 65 FR 35069, 35072 (June 1, 2000).

> continue and, unless a use was canceled due to dietary risk concerns, EPA will consider requests (normally by petition) to modify or maintain a tolerance as an "import tolerance." EPA plans to use a variety of means to provide an opportunity for interested parties to support the modification or maintenance of a tolerance in these circumstances.[10]

EPA may allow for an import tolerance "provided that there is a need for the tolerance because the pesticide is used outside of the United States on commodities intended for the United States market and a proponent of the tolerance supplies sufficient data or information to demonstrate that a tolerance meets the food safety requirements of FFDCA."[11]

In this case, EPA is proceeding with tolerance revocation before cancellation of any registered pesticide uses. However, EPA should nonetheless provide an opportunity to consider and approve requests for chlorpyrifos import tolerances where the data and risk assessments confirm that such tolerances would meet the safety standard. The D.C. Circuit Court of Appeals reversed a previous EPA decision to revoke all import tolerances along with all other tolerances for the product carbofuran, where the Agency agreed that exposure to carbofuran from imported foods alone met the safety standard.[12]

EPA's risk findings in the August 2021 rule support the retention of import tolerances. EPA characterized the risks from aggregate exposures from dietary (food) exposure; non-occupational, non-dietary (residential) exposures; and drinking water. In the August 2021 decision, EPA found that "exposures from food and non-occupational exposures individually or together do not exceed EPA's levels of concern."[13] However, EPA found that, unless chlorpyrifos uses were limited to certain uses as discussed above, the calculated additional exposures from drinking water exceeded levels of concern.[14]

These findings indicate that potential exposures from imported commodities would not exceed levels of concern. Imported commodities have exposure profiles that differ from those of domestic commodities. Among other factors, drinking water exposure assessments consider the application of the pesticide product for certain uses and in certain geographic areas. In the August 2021 rule, EPA acknowledged not only that drinking water exposure depends on the scope of permitted use within the United States, but also that limiting the domestic food use of chlorpyrifos to the eleven uses discussed above would result in lower drinking water exposures and in aggregate exposure levels that do not exceed levels of concern.[15] If EPA's decision to eliminate *all* domestic food uses remains in place, that would further reduce drinking water

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[10] *Id.*
[11] *Id.*
[12] *Nat'l Corn Growers Ass'n v. E.P.A.*, 613 F.3d 266, 275 (D.C. Cir. 2010); *see also* 40 CFR 180.254 (identifying retained import tolerances for carbofuran on certain commodities).
[13] *Id.* at 48332-33.
[14] *Id.* at 48333.
[15] *Id.*

exposures below levels of concern. In either case, allowing tolerances for imported commodities where needed should not create exposures above levels of concern.

C. EPA Should Provide A Clearer And More Practical Approach For Existing Stocks Of Chlorpyrifos Products Affected By The Tolerance Revocations

EPA's decision revokes tolerances for residues of chlorpyrifos on food and food commodities, but it need not and should not be implemented in a way that unduly burdens non-food uses, such as use on golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products. FIFRA explicitly recognizes the importance of EPA addressing the disposition of existing stocks of pesticides when registrations are canceled (FIFRA Sections 6 and 19) and to that end EPA developed a policy in 1991 providing a framework to determine existing stocks provisions on a case-by-case basis (56 Fed. Reg. 29362). Yet EPA's August 2021 decision does not address cancellation or the issue of existing stocks, and in particular it does not provide a clear path forward for products labeled for both food and non-food uses after the tolerances are revoked.

Requirements for existing stocks are normally addressed in connection with a cancellation order, but the Agency has provided no timetable for acting on cancellation or issuing such an order, and that appears unlikely to occur before the tolerances are revoked. This creates confusion for registrants, distributors, applicants and the public regarding the appropriate uses of chlorpyrifos.

EPA's recently posted frequently asked questions guidance on this issue is ambiguous and unworkable. The guidance states that the tolerance rule "does not prohibit sale and distribution of registered pesticide products," but also that "sale and distribution of chlorpyrifos products labeled for use on food products would be considered misbranded" and a "violation of FIFRA once the tolerances are revoked"[16] In other words, according to EPA, the rule *does* effectively prohibit sale of registered products whose labels include food uses. The legal basis for this position is unclear. Courts have rejected other efforts by EPA to prohibit sale of a registered product by declaring it "misbranded."[17]

The guidance also acknowledges that there are labels and registrations that contain both food and non-food uses, and suggests that "[f]ollowing cancellation," such labels "will need to be amended to remove any food-uses that were cancelled." However, cancellation is unlikely to occur before the tolerances are revoked and future cancellation would not render an existing registered product "misbranded." Thus, the legal status of these products after the tolerances are revoked will remain unclear.

CLA and RISE request that the Agency revisit its approach and provide a clearer and more practical path forward for existing stocks that encourages compliance with the tolerance

[16] Frequent Questions about the Chlorpyrifos 2021 Final Rule, available at https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule#question-10.
[17] *Reckitt Benckiser Inc. v. E.P.A.,* 613 F.3d 1131 (D.C. Cir. 2010); *Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d 34, 43 (D.D.C. 2011).

revocations while avoiding unnecessary marketplace confusion, needless legal jeopardy, wasted product and product disposal issues, excessive relabeling costs, and delays. The Agency could consider practical approaches short of full relabeling, such as stickers and point of sale notices, to allow existing stocks of registered products that are labelled for food and non-food uses to continue to be sold for uses that are unaffected by the tolerance revocation.

D. EPA's Decision Does Not Properly Respond To Comments And Fails To Provide Adequate Due Process

The implementation challenges above highlight the lack of public involvement in this decision. EPA's issuance of a final rule revoking all chlorpyrifos tolerances without providing a further opportunity for notice and comment, and without responding to prior comments, raises substantial due process concerns. The fact that the Ninth Circuit required "immediate issuance of a final regulation" "without further notice and without further period for public comment" limited the Agency's options, but does not eliminate its due process obligations. If anything, this unusual posture calls for heightened attention and a more robust process going forward. Given the six-month window before the rule is slated to go into effect, the Agency must act promptly to respond to these objections and to other objections it receives and to revise the final rule as warranted.

Particularly troubling is the fact that EPA revoked all chlorpyrifos tolerances without responding to comments from the public on prior proposals that bear directly on whether tolerances should be retained or revoked in the final rule. Although EPA requested comments on its November 2015 proposed rule to revoke tolerances, the Agency never responded to the over 90,000 comments it received and explicitly declined to do so in this rule.[18]

To provide adequate due process, publishing a decision for notice and comment is insufficient. EPA must also respond to those comments. Without an Agency response, EPA denies the public a meaningful opportunity for involvement in the rulemaking. The claim that EPA need not respond to comments on a proposed rule to revoke tolerances in issuing a final rule revoking the tolerances renders the comment process irrelevant. EPA likewise contends that relevant comments received as part of the registration review process are "separate and apart from the procedural process of this final rule action."[19] The Agency's assertion that *all* such comments will be addressed as part of the "ongoing registration review process" is not adequate assurance as the Agency has already stated its intent to cancel registrations for uses corresponding to the revoked tolerances. EPA's failure to respond to comments is inconsistent with the obligations of due process and transparency.

EPA's lack of commitment to due process in this regulatory action is also evident in its statements regarding the process for handling objections to the August 2021 rule. The rule cautions that "EPA will not consider any legal or factual issues presented in objections, if that issue could reasonably have been raised earlier in the Agency's review of chlorpyrifos relative to

[18] https://www.regulations.gov/document/EPA-HQ-OPP-2015-0653-0001
[19] 86 Fed. Reg. at 48334.

this petition."[20] However, without notice of the final rule, there was no opportunity for comments and objections targeted to the actual approach EPA has taken. There was also no notice to stakeholders of the proper forum among the many ongoing proceedings (petition to cancel, registration review, legal actions) in which objections must be lodged. Furthermore, EPA provides no timeline for responding to objections and has not committed to doing so before the tolerance revocations go into effect. The August 2021 rule states only that "objections of a purely policy or legal nature will be resolved in the Agency's final order," although the August 2021 rule itself purports to be final.

EPA should commit to responding fully to objections before the tolerance revocations go into effect, should extend the effective date if necessary to do so, and should make all warranted revisions and adjustments to the final rule in response to comments and objections before the tolerance revocations go into effect.

E. EPA Has Not Identified How It Plans To Harmonize The Tolerance Revocations With FIFRA

The FFDCA requires harmonization with FIFRA and EPA must coordinate tolerance revocations with FIFRA requirements.[21] EPA's decision to revoke chlorpyrifos tolerances provides no explanation as to how and when EPA plans to complete this harmonization. As the tolerance revocation is effective at the end of February 2022 and EPA is not expecting to complete registration review by the time the tolerance revocations are effective, growers and others affected by this decision need guidance on how to proceed during the interim period. Among many issues, EPA's failure to harmonize its tolerance and registration actions exacerbates confusion regarding label requirements and the status of existing stocks.

EPA should promptly provide information on how it plans to harmonize its tolerance rule with FIFRA registration decisions. CLA and RISE will comment further as needed once EPA announces its approach to FIFRA registrations related to this tolerance rule.

F. EPA's Decision Is Overly Conservative

The challenges outlined above all arise from an overly conservative decision. EPA's approach here is unnecessary given the available science, and appears to ignore the risk assessment undertaken by EPA's own career scientists. The broad approach taken by the Agency is detrimental to the regulatory process and the public. Instead of basing its decision on the available science, EPA has taken an overly cautious approach and revoked all chlorpyrifos tolerances based on "uncertainty" raised by epidemiology data EPA was unable to fully evaluate. The Agency's decision sends a disturbing message to other regulators around the world. EPA and the United States have long held a critical leadership role among countries implementing and defending evidence-based and risk-based regulation. The Agency should not allow this decision

[20] *Id.* at 48316.
[21] *See* Section 408(l) of the FFDCA, 21 U.S.C. Section 346a(l).

to be seen as a step away from its long-standing defense of these pillars of scientific integrity and sound regulation.

G. EPA Guidance On "Reasonable Grounds" Is Needed

The Agency should take concrete steps to avoid further confusion over the standards that apply to EPA's disposition of tolerance revocation petitions. The *LULAC* decision relied on EPA's regulation at 40 CFR 180.32(b), which requires petitions to modify or revoke a tolerance or tolerance exemption to provide "reasonable grounds." The Court confirmed that "[u]nder its regulations EPA may deny a petition when it finds that a petition is not supported by 'reasonable grounds' for revocation."

For greater clarity, consistency and predictability, we respectfully request that EPA develop and publish guidance on what constitutes "reasonable grounds" under 40 CFR 180.32(b). The Agency has repeatedly expressed its commitment to scientific integrity and improved outreach to the public.[22] Clear guidance regarding how EPA will consider such petitions will help ensure that they are used for their intended purpose – to bring to the Agency's awareness legitimate food safety concerns that may not be otherwise addressed through the pesticide regulatory process. Such guidance can assist the Agency in addressing future petitions in a timely and appropriate manner, applying rigorous scientific standards to them, and communicating outcomes to the public and the regulated community in a way that strengthens public confidence in the regulatory process.

* * * * * * * *

Thank you for your consideration of, and responses to, these objections, our request for a stay, and our request that EPA develop and publish guidance on how it will implement its regulation at 40 CFR 180.32(b) concerning what constitutes "reasonable grounds" for petitions seeking to modify or revoke tolerances or exemptions from tolerance.

Sincerely,

Chris Novak
President and Chief Executive Officer
CropLife America

Megan Provost
President
RISE

[22] *See, e.g., Draft FY 2022-2026 EPA Strategic Plan*, 86 Fed. Reg. 74448 (Oct. 1, 2021).

I, Dr. Richard Reiss, declare as follows:

1. I am competent to provide the information in this declaration, and I have personal knowledge of all facts set forth herein.

Introduction

2. I understand that the U.S. Environmental Protection Agency ("EPA") has issued a Final Rule revoking all tolerances for the pesticide chlorpyrifos (the "Final Rule") and that there is a 60-day period for the filing of objections regarding the Final Rule. This declaration is provided in support of objections to the Final Rule submitted by Gharda Chemicals International, Inc.

My Credentials

3. I am a Group Vice President and Principal Scientist with the consulting firm Exponent. I am an Environmental Health Scientist with expertise in risk assessment, exposure assessment, environmental chemistry and fate, mathematical modeling, and applied statistics. I have worked on scientific issues associated with numerous environmental statutes and have expertise in areas of air quality modeling, drinking water assessment, and chemical risk assessment. A complete copy of my *curriculum vitae* is attached to this Declaration.

4. I have been conducting and reviewing drinking water assessments with respect to pesticides since 1998, and I have reviewed several chlorpyrifos drinking water assessments over the last decade. I have conducted such assessments for dozens of pesticides over this time period and provided comments on many of the major refinements to drinking water assessment methodology that EPA has considered over the years. In performing these assessments, I have used all of the major models that EPA uses for surface water and groundwater drinking water risk assessments, and I regularly interact with EPA on issues associated with drinking water exposure.

5. I have also been significantly involved in toxicity issues associated with chlorpyrifos. I have written a journal publication that analyzed chlorpyrifos toxicity data and estimated benchmark doses (BMDs) that represent the level at which chlorpyrifos and chlorpyrifos oxon cause 10% acetylcholinesterase inhibition, which is the basis that EPA regulates chlorpyrifos. I have also recoded the chlorpyrifos physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) model that EPA used to estimate points of departure (PODs) for chlorpyrifos risk assessment.

6. By way of background, I received a Bachelor of Science in Chemical Engineering from the University of California, Santa Barbara in 1989; a Master of Science in Environmental Engineering from Northwestern University in 1991; and a Doctor of Science in Environmental Health from Harvard University in 1994.

7. I am actively involved in several scientific societies, and I am the past-President of the Society for Risk Analysis, the leading scientific society devoted to the field of risk assessment. I was the Managing Editor of *Risk Analysis: An International Journal*, the leading scholarly journal for risk analysis from 2001-2008. I was the winner of the 2001 Chauncey Starr Award from the Society for Risk Analysis. This award recognizes a risk analyst less than forty years of age who has made major contributions to the field of risk analysis. In 2010, I was elected a Fellow of the Society for Risk Analysis. In 2018, I won the Outstanding Practitioner Award from the Society for Risk Analysis.

EPA's Drinking Water Assessment in Proposed Interim Decision (PID)

8. In December of 2020, EPA released a Proposed Interim Decision (PID) for chlorpyrifos that included a Drinking Water Assessment (DWA). Previous DWA assessments considered all registered chlorpyrifos uses, but the DWA in support of the PID considered a

subset of eleven uses that are considered critical/high benefit, including alfalfa, apples, asparagus, cherries, citrus, cotton, peaches, soybeans, strawberries, sugar beet, and wheat. It included an assessment of drinking water risks using a highly refined methodology following EPA's most recent guidance on refining drinking water exposure. Risks were estimated both assuming a 1X and 10X Food Quality Protection Act (FQPA) factor. In the Final Rule, EPA retained the 10X FQPA factor based on what EPA believes to be uncertainties in the literature on potential neurodevelopmental effects. The PID concluded that there are regions in the U.S. where drinking water risks are acceptable for chlorpyrifos uses for all eleven of the critical/high benefit crops as listed in Table 10 of the PID, which is titled "Agricultural Uses Proposed for Retention in Chlorpyrifos Labels with an FQPA Safety Factor of 10X."

9. Drinking water risk assessments combine an assessment of toxicity and estimation of exposure. In both aspects, the chlorpyrifos drinking water risk assessment in the 2020 DWA that supports the PID was highly refined and among the most advanced assessments ever conducted by EPA for a pesticide.

10. The exposure assessment in the 2020 DWA represents one of the most refined (Tier 4 refinement) drinking water analyses that EPA has conducted. EPA used its latest surface water modeling methods, including new scenarios that were developed in 2020. EPA also accounted for the portion of a watershed that used a particular crop and the portion of that cropped area that is potentially treated with chlorpyrifos. EPA uses the terms percent cropped area (PCA) and percent crop treated (PCT) to represent these factors. EPA also accounted for available surface water monitoring data by using the seasonal wave with streamflow adjustment and extended capability (SEAWAVE-QEX) model and sampling bias factors (SBFs).

11. The 2020 DWA utilized new guidance on conducting refined drinking water assessments. EPA used its September 2020 "Framework for Conducting Pesticide Drinking Water Assessments for Surface Water." The framework outlines a tiered process for conducting drinking water assessments that relies on increasing refinement of the underlying assumptions in the assessment. The 2020 DWA applies the highest level of refinement (Tier 4) that is laid out in the EPA guidance. A Tier 4 assessment produces the spatial and temporally resolved estimates and quantitatively uses monitoring data. Thus, the 2020 DWA used the best available science for assessing drinking water risks.

12. EPA took the unusual step of having nine EPA staff peer-review the 2020 DWA. I am familiar with many EPA drinking water assessments and other types of risk assessments. Typical EPA assessments do not include this level of peer review.

13. The chlorpyrifos drinking water exposure assessment was refined several times before 2020. The first assessment was conducted in 2011 using EPA's standard methods. An updated assessment was conducted in 2014 that estimated regionally derived estimates for the Pacific Northwest and the South Atlantic-Gulf, and the 2016 assessment provided a more complete regional assessment, but still had significant limitations. The 2020 update focused on high-benefit crops and refined the 2016 assessment by (a) incorporating new surface water modeling scenarios, (b) presentation of the entire distribution of community water systems PCA adjustment factors and integration of state level crop treated data using PCT factors, and (c) quantitative use of surface water monitoring data.

14. In the 2020 DWA, EPA assumed that, for most drinking water systems, any chlorpyrifos that reaches a drinking water treatment system is converted to chlorpyrifos oxon via chlorination. Chlorpyrifos oxon is the active moiety that inhibits acetylcholinesterase (AChE),

an enzyme involved in neurotransmission. In our bodies, chlorpyrifos is partially metabolized to chlorpyrifos oxon, which results in AChE inhibition. For a smaller set of drinking water facilities that do not use free chlorine as a disinfectant, EPA assumed that chlorpyrifos was unconverted in the drinking water system.

15. In the 2020 DWA, to estimate points of departures (PODs) for risk assessment, EPA conducted one of the most advanced analyses that I am familiar with. PODs are a measure of the toxicity of the chemical and represents, in the case of chlorpyrifos, a level that is not considered toxic to a typical individual. EPA applied uncertainty factors to the POD to account for variability within the human population. To estimate PODs for chlorpyrifos and chlorpyrifos oxon, EPA used a physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) model that was developed by Corteva Agriscience over the course of more than a decade and was reviewed by the EPA Scientific Advisory Panel (SAP) several times. The PBPK/PD model simulates a dose of chlorpyrifos or chlorpyrifos oxon in the body and models its metabolism, tissue partitioning and clearance, and quantifies inhibition of AChE to estimate PODs. It represents one of the most advanced methodologies to estimate PODs.

16. After the substantial refinements described above, EPA concluded in the PID that there were regions in the U.S. where the drinking water risks were acceptable even with the application of the FQPA 10X factor. Therefore, the latest risk assessment produced by EPA concludes that there are acceptable drinking water risks for the eleven high-benefit crops.

17. In the Final Rule, EPA stated that it could not rely on the 2020 DWA for the following reason:

> When assessing different combinations of only those 11 uses in specific geographic regions, the modeling assumed that chlorpyrifos would not be labeled for use on any other crops and would not otherwise be used in those geographic regions. At this time, however, the currently registered chlorpyrifos uses go well beyond the 11 uses in the

> specific regions assessed in the 2020 DWA. Because the Agency is required to assess aggregate exposure from *all* anticipated dietary, including food and drinking water, as well as residential exposures, the Agency cannot rely on the 2020 DWA to support currently labeled uses.

86 Fed. Reg. 38315, 48,333 (Aug. 30, 2021). However, the 2020 DWA followed the most recent guidance from EPA on conducting the most highly refined regional drinking water assessments and represents the best available science. Further, EPA's reasoning does not make sense. Based on my decades of experience, the Agency routinely conducts assessments that presume what the use pattern will be upon a registration decision. This is fundamental to the Agency registration process. For example, for a new product, EPA conducts an assessment that assumes a set of proposed uses. The 2020 DWA was much like such an assessment for a new product. It presumed that only eleven crop uses may exist and conducted an assessment as such. The quote above references "*all* anticipated" exposures. The latest discussions between registrants and EPA focused on the eleven high-benefit crops; thus, those crops represent the set of "anticipated" uses. Thus, there is no scientific reason why the 2020 DWA could not form the basis of a decision on the future of those eleven crops and only those eleven crops.

18. Corteva commented on the lack of refinement in the 2016 DWA that EPA is now relying on (Corteva, 2017). For example, in the 2016 DWA, EPA used a PCA of 1, which unrealistically assumes that an entire watershed is planted with the crop that is being considered. This assumption was refined in the 2020 DWA. The 2020 DWA used both maximum regional-specific PCA values and it also used the full distribution of PCAs from the majority of the approximately 6500 drinking water treatment intakes from the EPA Office of Water Drinking Water Information System.

19. For the PID, EPA conducted a highly refined drinking water risk assessment for the 11 high-benefit crops. The assessment was refined over the course of nearly a decade and

utilized some of the most advanced risk assessment methods ever utilized by the Agency for a pesticide. The assessment went through substantial internal EPA peer-review. The result was that there are regions of the U.S. where there are acceptable drinking water risks for all eleven critical/high benefit crops even with the application of an FQPA 10X.

20. It should also be considered that even the 2020 DWA is overly conservative. EPA's standard index reservoir scenario for assessing drinking water risk is based on a small watershed in Shipman, Illinois that has an upper percentile drainage area to normal capacity (DA/NC). A high-end DA/NC means that there is large watershed drainage area relative to the volume of the reservoir. While it may be reasonable to base the index reservoir on a high-end DA/NC, EPA combines this assumption with several other factors to create a scenario that is not realistic even of the highly vulnerable Shipman reservoir.

21. For example, it unrealistically assumes that all applications in a watershed occur at the same time. For a scenario where two applications of chlorpyrifos are allowed per year with a 7-day treatment interval, the EPA standard scenario assumes that all first applications in the watershed occur on the same day and all second applications occur seven days later. It repeats this same assumption over a 30-year simulation.

22. EPA's standard methods for estimating drinking water concentrations produces conservative estimates of real-world chlorpyrifos and chlorpyrifos oxon drinking water concentrations even after the significant refinements that EPA made in the 2020 DWA.

Chlorpyrifos Oxon Drinking Water Study

23. EPA said that its 2020 DWA "assumed 100% conversion of chlorpyrifos to the more toxic chlorpyrifos oxon" EPA's 2020 Third Revised Chlorpyrifos Human Health Risk Assessment at 10. However, Corteva submitted a new chlorpyrifos oxon drinking water study in

December of 2020, around the time the PID was released, and provided EPA with interim study results in August of 2020. The results of the study were not considered in the PID despite EPA being aware of the study. EPA was consulted on the design of the study and provided feedback to Corteva. The interim results were presented to EPA before the issuance of the PID. The study is not onerous to review or interpret, and EPA could have done so before the issuance of the PID and certainly well before the issuance of the Final Rule.

24. The study dosed rats via drinking water with chlorpyrifos oxon for twenty-one days at concentrations as high as the solubility limit of chlorpyrifos. The reason for using the solubility limit of chlorpyrifos to set the chlorpyrifos oxon dose was that the oxon is assumed to potentially occur in drinking water through conversion of chlorpyrifos to chlorpyrifos oxon. Therefore, the chlorpyrifos oxon concentration in drinking water cannot be higher than the chlorpyrifos concentration.

25. The study measured AChE inhibition in red blood cells (RBCs), brain, and in several other tissues. While it is widely used as a marker of exposure, RBC AChE inhibition is not considered to be of direct biological significance. EPA regards RBC AChE inhibition as a "surrogate" for peripheral nervous system AChE inhibition. Brain AChE inhibition is the relevant endpoint for any potential neurotoxicity.

26. A prior study showed that even a very high dose of 10 mg/kg of chlorpyrifos oxon given orally did not cause measurable brain AChE inhibition even though the same dose of chlorpyrifos caused 48% brain AChE inhibition. This result shows that, given by the oral route, the oxon is a less potent inhibitor of brain AChE than parent chlorpyrifos. It is likely that the relative difference in brain AChE for chlorpyrifos and chlorpyrifos oxon is the result of a lack of systemic bioavailability of the oxon. The lack of systemic bioavailability is likely due to

significant hydrolysis in the gastrointestinal tract and portal vein, substantial first-pass metabolism in the liver, and additional loss in circulation due to interactions with plasma and RBC cholinesterases. All of this limits access of chlorpyrifos oxon to peripheral tissues such as the brain, which is where AChE inhibition is relevant.

27. The chlorpyrifos oxon drinking water study found (a) no detectable circulating chlorpyrifos oxon in blood, (b) no statistically significant AChE inhibition in either RBC or brain, and (c) an absence of clinical signs of toxicity or markers of exposure.

28. Given that the oxon drinking water study was conducted at the limit that the oxon could be present in drinking water is of regulatory significance. It shows that even at the limit that the oxon could be present in drinking water, neither RBC AChE nor brain AChE, the two compartments of regulatory interest to EPA, were inhibited.

29. The demonstration that the oxon has even less potential to inhibit brain AChE, the true target for potential neurotoxicity, than parent chlorpyrifos is further evidence that oxon concentrations in drinking water are not a risk concern. Thus, EPA incorrectly assumed in the 2020 DWA that chlorpyrifos oxon is more toxic than the parent chlorpyrifos for drinking water exposure purposes.

30. The oxon drinking water study shows that drinking water risks associated with the oxon are not a risk concern for any agricultural uses of chlorpyrifos and should not be part of the EPA's aggregate risk assessment or serve as a basis for limiting uses of chlorpyrifos.

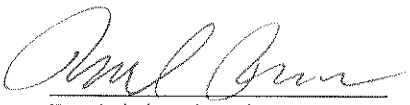
Import Tolerances

31. In the Final Rule, EPA also canceled all import tolerances for chlorpyrifos. However, the only risk associated with imported food is dietary exposure from food residues. EPA's assessment clearly shows that dietary risk is not of concern even with the 10X FQPA

factor. Drinking water, bystander, or occupational exposure risks are not relevant for import tolerances. Therefore, EPA's assessment provides no scientific basis for canceling import tolerances. In fact, the assessment confirms the opposite – there is no risk associated with imported food.

I, Dr. Richard Reiss, declare that the forgoing statement are true and correct to the best of my knowledge.

Dated: October 21, 2021



Dr. Richard Reiss

APPENDIX A

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Professional Profile

Dr. Reiss is an environmental health scientist with expertise in risk assessment, exposure assessment, environmental chemistry and fate, mathematical modeling, and applied statistics. He provides consulting services related to scientific issues associated with numerous environmental statutes, and has expertise in both air quality and chemical risk assessment. He has conducted risk assessments, data analyses, probabilistic exposure modeling, and environmental exposure modeling for environmental agents, such as pesticides, industrial chemicals, and consumer product chemicals. He has conducted risk assessments for new and existing products.

Dr. Reiss is very active in the application and development of quantitative methods in risk assessment. He is the developer of the Probabilistic Exposure and Risk assessment model for FUMigants (PERFUM), which is an air dispersion model designed to evaluate bystander inhalation exposure following fumigant applications. PERFUM is widely used by Environmental Protection Agency (EPA) and other public agencies for evaluating bystander risks for pesticide volatilization. Generally, he has used a variety of mathematical models in conducting occupational and ecological risk assessments for pesticides and industrial chemicals; and performed statistical analyses, including dose-response modeling to evaluate chemical toxicity. He has published in the areas of human and ecological risk assessment, exposure assessment, dose-response, nutrition, and epidemiology.

Dr. Reiss is actively involved in several scientific societies and he is the Past-President and Fellow of the Society for Risk Analysis (SRA), the leading scientific society devoted to the field of risk assessment. Dr. Reiss was the Managing Editor of Risk Analysis: An International Journal, the leading scholarly journal for risk analysis, from 2001 through mid-2008. He was the winner of the 2001 Chauncey Starr (early career) award from SRA. In 2018, he was awarded the Outstanding Practitioner Award from SRA.

Academic Credentials & Professional Honors

Sc.D., Environmental Health, Harvard University, 1994

M.S., Environmental Engineering, Northwestern University, 1991

B.S., Chemical Engineering, University of California, Santa Barbara, 1989

Outstanding Practitioner Award from the Society for Risk Analysis, 2018, recognizing a scientist with an outstanding risk assessment practice.

Chauncey Starr Award from the Society for Risk Analysis, 2001, recognizing a scientist under 40 years of age who has made significant contributions to risk analysis

Outstanding Service Award, Society for Risk Analysis, 2009

Leslie Silverman Scholarship, Harvard University, 1991

Walter P. Murphy University Fellowship, Northwestern University, 1989-1990

Prior Experience

Vice President, Sciences International, 2000-2006

Senior Scientist, Quantitative Risk Assessment Expert, Jellinek, Schwartz & Connolly, Inc., 1998-2000

Senior Air Quality Analyst, Sonoma Technology, Inc., 1994-1998

Engineer, Environmental Solutions, Inc., 1990-1991

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE ADMINISTRATOR

In re:	
Revocation of All Tolerances for Chlorpyrifos	FFDCA-HQ-2021-0001 (EPA-HQ-OPP-2021-0523)
.	BUSINESS CONFIDENTIALITY ASSERTED

GHARDA CHEMICALS INTERNATIONAL, INC.'S OBJECTIONS TO THE FINAL RULE REVOKING ALL TOLERANCES FOR CHLORPYRIFOS

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Chlorpyrifos Registrant

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I. INTRODUCTION

On August 30, 2021, the U.S. Environmental Protection Agency ("EPA" or the "Agency") issued a final rule revoking all tolerances for the pesticide chlorpyrifos. *Final Rule for Chlorpyrifos Tolerance Revocations*, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"). Pursuant to Section 408(g)(2)(A) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 346a(g)(2)(A), and 40 C.F.R. part 178, *et seq.*, Gharda Chemicals International, Inc. ("Gharda") submits these objections to EPA's Final Rule, together with the accompanying Petition to Stay the Effective Date of the Revocation of All Tolerances for Chlorpyrifos.

EPA issued the Final Rule in response to an April 29, 2021 order of the U.S. Court of Appeals for the Ninth Circuit in the lawsuit *League of United Latin American Citizens v. Regan*, 996 F.3d 673, 678 (9th Cir. 2021) ("LULAC"), instructing EPA to "either to modify chlorpyrifos tolerances and concomitantly publish a finding that the modified tolerances are safe," "or to revoke all chlorpyrifos tolerances." Rather than modify tolerances consistent with the finding of its expert scientists that a subset of eleven key crop uses in select regions are safe, as set forth in the Agency's December 2020 Proposed Interim Decision for Chlorpyrifos, EPA-HQ-OPP-2008-0850-0971 ("PID"), EPA chose to revoke *all* tolerances for chlorpyrifos. EPA did so because it claimed that it is required under the FFDCA to assess aggregate exposure risks taking into account all "currently registered uses" and that, when taking into account potential drinking water exposures, it could not conclude that "the products as currently registered" are safe. Under the Final Rule, tolerances for all commodities will expire six months from the date of publication, on February 28, 2022. 86 Fed. Reg. at 48,336.

Gharda is challenging the legal and factual sufficiency of the Final Rule by exercising its right to file objections. Specifically, EPA has abused its discretion, acted arbitrarily and capriciously, and violated the due process rights of Gharda and others by revoking all

chlorpyrifos tolerances despite conceding in its own risk assessment that eleven key crop uses in select regions are safe, and in disregard of a written commitment from Gharda provided to EPA well in advance of the Final Rule to modify Gharda's registration in accordance with the Agency's safety finding.

Among other issues, the Final Rule is fatally flawed because it ignores relevant scientific data, including (i) comments on and proposed refinements to the 2016 drinking water assessment EPA relied on to revoke tolerances, (ii) the Agency's updated, more highly refined, and peer-reviewed 2020 drinking water assessment, and (iii) a drinking water study of chlorpyrifos oxon (the chlorpyrifos residue EPA believed to be of concern in drinking water) submitted by the registrants nearly a year ago that significantly undermines EPA's assumptions about drinking water risk concerns. EPA's failure to adequately consider and respond to highly relevant scientific data and comments that bear directly on the drinking water concerns EPA used to justify a revocation of all tolerances is arbitrary and capricious and raises significant due process concerns. EPA's Final Rule also improperly revoked import tolerances the Agency conceded in the PID are safe, and incorrectly applies a precautionary Food Quality Protection Act ("FQPA") safety factor of 10X to address "uncertainties" in epidemiology studies the Agency has acknowledged do not meet basic standards of reliability.

Apart from lacking any reasoned or logical scientific justification, the portions of the Final Rule objected to herein impose an unreasonable and effectively meaningless six-month implementation period. The six-month period for implementation ignores reality and allows no time for Gharda, distributors, and growers to phase out and exhaust significant stores of chlorpyrifos products that currently exist in the supply chain, and that will potentially cause the needless disposal of safe and nutritious food and feed. The disastrous consequences of the Final

Rule will ripple through the agricultural supply chain. EPA has also failed to harmonize the Final Rule with the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), including by abdicating its responsibility to oversee the safe, lawful, and orderly phase-out of inventories and existing stocks of chlorpyrifos products. The Agency also disregarded cancellation procedures and interagency review processes intended to notify the public and other affected parties of actions like the one taken here that will significantly impact the agricultural economy.

Finally, EPA's decision followed months of discussions with Gharda concerning a voluntary cancellation of uses, during which Gharda committed to meeting each of EPA's continually increasing and scientifically or statutorily unjustified demands, in a good-faith effort to cooperate with the Agency. EPA led Gharda to believe it was close to finalizing a voluntary cancellation agreement with EPA that would allow key crop uses to continue—key crop uses that *EPA had found safe* in the PID—when the Agency abruptly withdrew from these discussions, without an explanation to Gharda, and revoked all tolerances. EPA's conduct and processes leading up to the Final Rule ignored its own science, are fundamentally unfair and demonstrate bad faith, further undermining the reasonableness of the Agency's decision-making.

For these reasons and as outlined more fully below, and because of the significant, immediate, and irreparable injuries Gharda has and will continue to suffer as a result of the revocation of all tolerances, the Final Rule should be summarily reversed or, at a minimum, stayed pending administrative review by EPA and any potential judicial review of the objections submitted by Gharda, growers, grower groups, and other adversely affected stakeholders.

II. SUMMARY OF OBJECTIONS

As set forth more fully herein, Gharda objects to the Final Rule on the following grounds:

1. EPA acted arbitrarily and capriciously by revoking all chlorpyrifos tolerances despite conceding in its own risk assessment that eleven key crop uses in select regions are safe. In

doing so, EPA ignored its PID and the updated, refined 2020 drinking water assessment on which the PID relied, claiming it is required by the FFDCA to assess risks based on exposures from all "currently registered uses." EPA's decision and reasoning is at odds with the statutory text, which is forward-looking and instructs EPA to assess "anticipated" exposures, not exposures based on uses the Agency *previously* approved, and would lead to the absurd result that EPA could never modify tolerances to limit use of a previously registered product based on new or updated scientific data. Consistent with its repeated commitments to EPA prior to the Final Rule, Gharda respectfully requests that, at a minimum, EPA retain the tolerances for the eleven key crops found safe in the PID.

2. EPA acted arbitrarily and capriciously in disregarding a written commitment from Gharda to modify its registration in accordance with the Agency's safety finding. The Agency disingenuously claimed that its "ability to make the safety finding" for a limited combination of uses in certain geographic areas "would be contingent upon significant changes to the existing registrations, including use cancellations, geographical limitations, and other label changes." EPA had at its disposal a commitment for these exact "use cancellations, geographical limitations, and other label changes" and decided for reasons unrelated to science or its statutory obligations not to act on it.

3. EPA acted arbitrarily and capriciously and in bad faith in negotiating a voluntary cancellation with Gharda, during which Gharda met each of EPA's continually increasing and scientifically unjustified demands, and during which EPA misled Gharda to believe that some key crop uses would survive, only to then abruptly and inexplicably revoke all tolerances. EPA added insult to injury in its misleading and prejudicial public messaging around the Final Rule, which cited reasons for revocation that are unsupported by science and at odds with the language

of the Final Rule itself.

4. EPA acted arbitrarily and capriciously and abused its discretion in failing to give adequate consideration to relevant scientific data and information. These include (i) comments on and proposed refinements to the 2016 drinking water assessment EPA relied on to revoke tolerances, (ii) the Agency's updated, more highly refined, and peer-reviewed 2020 drinking water assessment EPA discarded in the Final Rule, and (iii) a drinking water study submitted by the registrant nearly a year ago that demonstrates that chlorpyrifos oxon in drinking water is not a risk concern, nullifying EPA's prior assumptions concerning the effects of drinking water exposure. EPA's failure to consider relevant scientific data and information has damaged the Agency's global reputation as a fair, independent, and science-driven regulatory body.

5. EPA's failure to adequately consider and respond to highly relevant scientific data and information that bear directly on the drinking water concerns EPA used to justify a revocation of all tolerances violates Gharda's legally protectable property right in its registration and raises significant due process concerns.

6. EPA's Final Rule revoking tolerances without any reasoned or logical scientific basis deprives Gharda of the economic value of its registration, infringing Gharda's substantive due process rights.

7. EPA acted arbitrarily and capriciously by imposing an unreasonably short, off-season implementation period for the Final Rule, without an appropriate scientific basis for doing so. This will result in devastating economic and other harms to Gharda and its distributors, not to mention the growers who purchased Gharda's products in reliance on the registration and who depend on chlorpyrifos as their primary effective and affordable crop protection tool.

8. EPA acted arbitrarily and capriciously in failing to harmonize its decision with FIFRA,

including by abdicating its responsibility to oversee the safe, lawful, and orderly phase-out of inventories and existing stocks of chlorpyrifos products that will soon be rendered unusable as a result of the Final Rule. EPA must, at a minimum, revise the Final Rule to extend the expiration date of chlorpyrifos tolerances coextensive with a meaningful period for the exhaustion of existing stocks.

9. EPA acted in an arbitrary and capricious manner in revoking import tolerances. EPA conceded in its PID and underlying risk assessment that there are no dietary (non-drinking water) exposure risks associated with chlorpyrifos use in the United States or from imported foods.

10. EPA acted arbitrarily and capriciously and abused its discretion in failing to seek review of its revocation decision by the Office of Management and Budget's Office of Information and Regulatory Affairs ("OIRA"), given the significant impact the Final Rule will have on the U.S. agricultural economy.

11. EPA acted arbitrarily and capriciously in applying a precautionary 10X FQPA safety factor to address "uncertainties" in epidemiology studies of neurodevelopmental effects that do not meet basic standards of reliability.

III. GHARDA AND ITS ROLE IN THE CHLORPYRIFOS MARKET

Established in 1967, Gharda is a research-based company leading in the field of agrochemical manufacturing. Declaration of Ram Seethapathi ("Seethapathi Decl.") ¶ 5. Gharda was founded by Dr. Keki Hormusji Gharda, a prominent chemical engineer and chemist. *Id.* After obtaining a Masters degree and Ph.D. in Chemical Engineering from the University of Michigan, Ann Arbor, Dr. Gharda established Gharda Chemicals in a small rented shed. *Id.* More than four decades of innovation and investment in R&D transformed Gharda into a successful pioneer agrochemical company. *Id.* Gharda's product portfolio includes a wide range of insecticides and herbicides, including chlorpyrifos, for which it holds an EPA registration.

Gharda sells end-use chlorpyrifos products under the brand name Pilot™ as well as technical grade chlorpyrifos for manufacturing use. *Id.*

Chlorpyrifos is a vitally important agricultural tool, protecting over fifty valuable U.S. food crops from destruction due to insect pests, including alfalfa, cotton, soybeans, sugarbeets, and wheat. *Id.* ¶ 6. Crops protected by chlorpyrifos are worth upwards of over a hundred million dollars annually to the U.S. economy. *Id.* (citing EPA, Revised Benefits of Agricultural Uses of Chlorpyrifos at 5, 7 , EPA-HQ-OPP-2008-0850-0969 (Nov. 18, 2020) ("Revised Benefits")). Chlorpyrifos has value to growers in protecting their crops and income, as well as value to consumers who enjoy affordable, healthy, and high quality produce throughout the year. *Id.*

Chlorpyrifos's critical importance as an insect pest management tool is due to its broad-spectrum efficacy, favorable environmental characteristics, and affordability for growers. *Id.* ¶ 7. It is the leading active ingredient to control a broad spectrum of difficult-to-control insect pests, and for some destructive pests it is the only effective pest management tool available. *Id.* (citing Revised Benefits at 2). Because of its broad-spectrum effectiveness, chlorpyrifos is often the first tool growers employ to control new or unknown insect pests, a long-standing problem but one that will be exacerbated by climate change. *See id.* ¶ 8 (citing Revised Benefits at 12–13) (removal of "broad-spectrum materials such as chlorpyrifos . . . from pest management programs can result in unexpected outbreaks of previously minor pests or even the emergence of new pests"). Chlorpyrifos is also less harmful to beneficial insect populations than other insecticides. *Id.* It also requires fewer applications and avoids the use of multiple chemistries to control certain pests, reducing overall insecticide use. *Id.*

Gharda has long supported the registration of chlorpyrifos in the United States, including through an industry task force that provided financial and other support for comments, scientific data, and other materials submitted to EPA by Dow AgroSciences, LLC, now Corteva Agriscience. *Id.* ¶ 9, Appendix A. Gharda has invested over Redacted - CBI in the development of data and other information to support the registration of chlorpyrifos in the United States.

In February 2020, Corteva announced that it would end production of chlorpyrifos by 2021. *Id.* ¶ 10. At that time, chlorpyrifos continued to be a critically important agricultural tool for many growers. *Id*. As a result, many distributors and farm input suppliers began looking to Gharda to meet the market demand for chlorpyrifos. *Id*. In response to this increase in demand, Gharda significantly increased its production of chlorpyrifos. *Id*. Immediately prior to the Final Rule, Gharda was the primary supplier of chlorpyrifos for agricultural use in the United States. *Id*.

Chlorpyrifos is one of Gharda's most important products. In 2020, Gharda's annual U.S. revenues of chlorpyrifos were approximately Redacted - CBI. *Id.* ¶ 11. Revenues from sales of chlorpyrifos comprise a significant portion of Gharda's overall U.S. business, which prior to the Final Rule was only expected to increase. *Id.* In 2020, Gharda's annual U.S. revenues from chlorpyrifos were approximately Redacted - CBI. *Id.* 2021 U.S. revenues from chlorpyrifos total Redacted - CBI to date and prior to the Final Rule were expected to increase to Redacted - CBI by year end. *Id.* In 2022 and beyond, Gharda's annual U.S. revenues from chlorpyrifos were projected (before the Final Rule) to be approximately Redacted - CBI annually. *Id.*

Gharda's position in the U.S. agrochemical industry is unique. *Id.* ¶ 12. Unlike many other registrants and leading suppliers of crop protection tools in the United States, Gharda does not have U.S.-based manufacturing facilities, which adds an additional level of complexity to the

supply chain not encountered by U.S.-based manufacturers. *Id*. Gharda ships materials to the United States and then uses tolling companies to package and label the technical and end use chlorpyrifos products for sale to U.S. distributors, creating significant employment opportunities. *Id*. The pandemic has exponentially increased the costs and time required to ship Gharda's materials to the U.S. for formulating, packaging, and labeling. *Id*.

Currently, Gharda has a significant volume of raw materials on hand at its manufacturing facility in India. *Id.* ¶ 13. Gharda also has inventory of U.S. labeled chlorpyrifos product on hand at its India facility valued at Redacted - CBI. *Id.* In addition, Gharda has inventories of chlorpyrifos product ready for distribution in the U.S. valued at Redacted - CBI. *Id.* If Gharda is unable to formulate, sell, and distribute these products for use in the 2022 growing season and beyond, Gharda will suffer Redacted - CBI economic losses. *Id.* These losses are in addition to the Redacted - CBI loss in its investment in chlorpyrifos and future annual lost sales of approximately Redacted - CBI annually. *Id.* There are also significant stores of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers, estimated to be valued at approximately Redacted - CBI. *Id.* ¶ 14. (Gharda has been specifically informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI. *Id.*)

IV. LEGAL STANDARDS

A. Tolerance Revocations Under the FFDCA

The FFDCA requires EPA to set food safety "tolerances," which are maximum levels of pesticide residue allowed in or on food. FFDCA § 408, 21 U.S.C. § 346a. EPA "may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe" and "shall modify or revoke a tolerance if the Administrator determines it is not safe." FFDCA § 408(b)(2)(A)(i), 21 U.S.C.

§ 346a(b)(2)(A)(i). Food containing pesticide residues that exceed an established tolerance level is deemed "adulterated" under the FFDCA and may not be moved in interstate commerce. FFDCA §§ 301, 402, 21 U.S.C. §§ 331, 342. In considering whether to establish, modify, or revoke a tolerance, EPA must consider, among other things, "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue." FFDCA § 408a(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D)(i).

In 1996, Congress amended the FFDCA with the passage of the FQPA, which, among other things, established a new safety standard for pesticide tolerances covering pesticide residues in or on raw agricultural commodities. A tolerance is deemed "safe" under the FFDCA if "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii). This includes exposure from food, drinking water, and in residential settings, but does not include occupational exposure. In assessing reasonable certainty of no harm, EPA is to apply an additional tenfold margin of safety "to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children" but EPA has discretion to apply a different margin of safety if there is "reliable data" to support that determination. FFDCA § 408(b)(2)(C)(i)(II) and (III); 21 U.S.C. 346a(b)(2)(C)(i).

While application of "reasonable certainty of no harm" to tolerances for raw agricultural commodities was new to EPA when the FQPA was passed, the same standard had been used for decades by EPA when establishing tolerances for processed foods and by the Food and Drug Administration ("FDA") in approving food additives, in both cases under FFDCA § 409. In the 1958 Food Additives Amendment to the FFDCA, Congress made clear that a safety

determination under the "reasonable certainty of no harm" standard does not require absolute proof of safety: "Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not—and cannot—require proof beyond any possible doubt that no harm will result under any conceivable circumstance." S. Rep. No. 2422, 85th Cong., 2d Sess. 6, *reprinted in* 1958 U.S.C.C.A.N. 5300, 5305; *see also* H.R. Rep. No. 2284, 85th Cong., 2d Sess. 4-5 (1958). Thus, Congress did not intend the reasonable certainty of no harm standard to be based on the precautionary principle, under which all doubt must be exhausted before a tolerance may be established or left in effect.

Consistent with this standard, tolerances cannot be revoked without valid and reliable data because registrants have a legally protectable property interest in their registration, which cannot be taken away without due process of law. *See Indus. Safety Equip. Ass'n v. EPA*, 656 F. Supp. 852, 856 (D.D.C. 1987), *aff'd*, 837 F.2d 1115 (D.C. Cir. 1988) ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law."); *Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."); *Ctr. for Biological Diversity v. EPA*, No. 11-cv-00293, 2013 WL 1729573, at *6–7 (N.D. Cal. Apr. 22, 2013) ("[O]wners of the pesticide registrations . . . have property and financial interests in the registrations."); *Mem. & Order, Pesticide Action Network N. Am. v. EPA*, No. C 08-01814, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce, distribute and sell pesticides . . . [and] therefore constitute property[.]"). It is therefore essential that the Agency have valid and reliable data and conduct a thorough, science-based assessment before making a decision to modify or revoke tolerances.

B. Objections Under the FFDCA

Under Section 408(g) of the FFDCA, "[w]ithin 60 days after a regulation or order is issued" by EPA, "any person may file objections thereto with the Administrator, specifying with particularity the provisions of the regulation or order deemed objectionable and stating reasonable grounds therefore." 21 U.S.C. § 346a(g)(2)(A). Objections must (1) "[b]e in writing"; (2) "[s]pecify with particularity the provision(s) of the order, regulation, or denial objected to, the basis for the objection(s), and the relief sought"; (3) "[b]e signed by the objector"; (4) "[s]tate the objector's name and mailing address"; (5) "[b]e submitted to the hearing clerk"; and (6) "[b]e received by the Hearing Clerk not later than the close of business of the 60th day following the date of the publication in the Federal Register of the order to which the objection is taken …." 40 C.F.R. § 178.25.

V. RELEVANT BACKGROUND AND REGULATORY HISTORY

A. EPA's 2020 Proposed Interim Decision

On December 7, 2020, as part of EPA's Registration Review of chlorpyrifos, EPA published its PID. *See* 85 Fed. Reg. 78,849 (Dec. 7, 2020). The PID is supported by analyses included in EPA's September 21, 2020 Third Revised Human Health Risk Assessment, EPA-HQ-OPP-2008-0850-0944 (the "2020 RHHRA"), which in turn relies on, among other documents, a September 15, 2020 Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review, EPA-HQ-OPP-0850-0941 (the "2020 DWA"). EPA's PID and 2020 DWA reflected a fulsome, measured, and well-reasoned assessment of the human health and drinking water risks of chlorpyrifos by EPA's expert scientists.

In its 2020 RHHRA and PID, EPA continued to use 10% red blood cell acetyl cholinesterase inhibition ("RBC AChE") as a regulatory endpoint or point of departure for human health risk assessments for chlorpyrifos. *See* 2020 RHHRA at 2. This conservative and

health-protective endpoint is supported by decades of scientific study. EPA stated that it "remains unable to verify the reported findings" of epidemiology studies claiming links between prenatal exposure to chlorpyrifos and neurodevelopmental effects. *Id.* at 89–90.

EPA's PID relied on the 2020 DWA, which updated and refined the Agency's 2016 DWA. The 2020 DWA is one of the most sophisticated drinking water analyses EPA has conducted, and relied on EPA's most cutting edge and highly refined methods for assessing drinking water risks. *See* Declaration of Rick Reiss ("Reiss Decl.") ¶¶ 9–11. EPA subjected the 2020 DWA to peer review by nine EPA expert scientists, an unprecedented level of peer review for an assessment of its kind. *Id.* ¶ 12. In the 2020 DWA, EPA focused on eleven uses (alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugar beet, strawberry, and wheat) that EPA determined to be high-benefit, critical crop uses. *Id.* ¶ 8. The 2020 DWA focused on select regions of the country where estimated drinking water concentrations are below the drinking water level of concern. *Id*.

In the 2020 RHHRA and PID, EPA conducted an assessment of potential risk to human health from aggregate exposure to chlorpyrifos residues, taking into account all anticipated dietary exposures from food, drinking water, and residential sources, pursuant to FFDCA Section 408(b). EPA determined that there were *no* potential risks of concern from exposure to chlorpyrifos in food or residential uses alone. 2020 RHHRA at 12; PID at 14, 18. EPA determined that risks from drinking water exposure exceeded safe levels taking into account *all* registered uses but, relying on its 2020 DWA, EPA found that risks were *below* the drinking water level of concern benchmark anticipating use only on the eleven high-benefit crops set forth above in certain identified regions of the country. PID at 18.

In its 2020 RHHRA and PID, EPA presented two potential approaches for assessing potential risks: (i) application of a 10X FQPA safety factor and limiting use of chlorpyrifos to the eleven high-benefit agricultural uses in select regions of the country due to "uncertainty" in "the science addressing neurodevelopmental effects," or (ii) application of a 1X FQPA safety factor, which would allow for the retention of all currently registered uses. Regarding the first approach, EPA was unequivocal that "the agency has determined" that limiting use to the eleven "high-benefit agricultural uses" in the select geographic regions "**will not pose potential risks of concerns with an FQPA safety factor of 10X**." PID at 40 (emphasis added). EPA committed to "consider registrant and stakeholder input on the subset of crops and regions from the public comment period" and stated that it may conduct further analysis to determine if any other limited uses may be retained." *Id.* EPA also indicated that it may further refine its assessment based on feedback and recommendations from the September 2020 FIFRA Scientific Advisory Panel. *Id.*

Gharda submitted comments on the PID on February 3, 2021. EPA-HQ-OPP-2008-0850-0999. Gharda urged that the weight of the scientific evidence supported application of a 1X FQPA safety factor, and urged EPA to consider a Corteva drinking water study of chlorpyrifos oxon submitted to the EPA on December 4, 2020, which shows that there are no drinking water risk concerns associated with chlorpyrifos oxon. *See A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days*, MRID 51392601; *see also* Reiss Decl. ¶¶ 23–30.

B. Gharda's Discussions with EPA Concerning a Potential Voluntary Cancellation of Chlorpyrifos Uses

1. *Initial Discussions Focus on a Potential Voluntary Cancellation of 1X Crop Uses*

In April 2021, EPA regulatory personnel reached out to Gharda to discuss whether Gharda would entertain an agreement to voluntarily cancel some uses of chlorpyrifos.

Seethapathi Decl. ¶ 21. These discussions focused initially on uses identified in the PID as the 1X uses. *Id*. EPA proposed a meeting with Gharda on April 20, 2021, and requested that Gharda confirm in writing in advance of that meeting Gharda's commitment to voluntarily cancel the 1X uses (while retaining the eleven high benefit crop uses identified as the 10X uses). *Id*. In response, even though Gharda was confident that all 1X uses are well supported, Gharda indicated that it would consider phasing out some 1X uses on a reasonable timetable and adopting potential geographic restrictions on crop uses and other risk mitigation measures. *Id.* & Ex A. Gharda expressed concern with the Agency's proposed rushed timetable, however, given the impact of a phase-out on its business and on the grower community, and given that EPA had not yet reviewed comments on the PID. *Id*. EPA cancelled the meeting with Gharda in order to discuss Gharda's letter further internally. *Id*.

On April 29, 2021, the Ninth Circuit issued a decision in *LULAC*, which concerned EPA's handling of an administrative petition to revoke all tolerances filed by several nongovernmental organizations. In a 2-1 decision, a three-judge panel of the Ninth Circuit held that EPA's denial of objections to a 2017 order denying the administrative petition was at odds with the FFDCA because EPA did not make an affirmative finding that chlorpyrifos tolerances were "safe" in response to the petition, outside of its normal regulatory processes. *LULAC*, 996 F.3d 673 (9th Cir. 2021). The Ninth Circuit ordered EPA "either to modify chlorpyrifos tolerances and concomitantly publish a finding that the modified tolerances are safe," "or to revoke all chlorpyrifos tolerances." *Id.* at 678. (emphasis added). In making this ruling the court expressly recognized the importance of the PID. Indeed, the court stated that:

> [D]uring the pendency of this proceeding, in December 2020, the EPA issued a Proposed Interim Registration Review Decision proposing to modify certain chlorpyrifos tolerances. The EPA also convened another SAP [Scientific Advisory Panel] in 2020. **If, based upon the EPA's further research the EPA can now**

> **conclude to a reasonable certainty that modified tolerances or registrations would be safe, then it may modify chlorpyrifos registrations rather than cancelling them**.

Id. at 703 (emphasis added). The court also ordered EPA to "correspondingly modify or cancel related FIFRA registrations for food use in a timely fashion consistent with the requirements of 21 U.S.C. § 346a(a)(1)." *Id.* at 678.

2. *EPA's Progressively Increasing Demands that Gharda Agree to Cancel Additional Uses and Application Methods*

After the Ninth Circuit issued its decision in *LULAC*, EPA reached back out to Gharda to resume discussions about a potential voluntary cancellation of chlorpyrifos uses. Seethapathi Decl. ¶ 34. EPA career supervisory personnel strongly urged Gharda to agree to voluntarily cancel the 1X uses and emphasized that the Agency had limited time to decide how to implement the court's decision. *Id.* In response, Gharda expressed its disagreement with the Ninth Circuit decision and hope that EPA would seek rehearing of and/or appeal the flawed decision. *Id.* & Ex. B. Nevertheless, in a good-faith effort to work cooperatively with EPA and believing it had little choice but to accept voluntary cancellation terms, Gharda committed to voluntarily cancel yet additional 1X agricultural uses, pursuant to scheduled phase-outs and with appropriate existing stocks orders. *Id.* EPA strongly implied during these discussions that the 10X uses would remain in place as long as Gharda voluntarily cancelled all 1X uses. *Id.*

In further discussions with EPA career supervisory personnel in late May 2021, EPA expressed to Gharda that it was willing to consider retention of only the 10X uses, and reiterated that it was under pressure to act quickly as a result of the Ninth Circuit decision. *Id.* ¶ 24. EPA urged Gharda to confirm in writing its agreement to voluntarily cancel all 1X uses. *Id.* In response, and even though such a reduction in uses would eliminate more than 50% of Gharda's U.S. chlorpyrifos business, Gharda committed to continue working in good faith with EPA

towards an agreement to voluntarily cancel all 1X uses. *Id.* & Ex. C. To that end, **on June 7, 2021, Gharda confirmed in writing to EPA that it would voluntarily cancel all currently approved agricultural uses of chlorpyrifos, other than the uses identified in the PID as 10X uses**. *Id*. In turn, Gharda requested that EPA (i) work with it to address the orderly exhaustion of its existing inventories, particularly given its unique role in the U.S. agrochemical industry; (ii) agree on orderly processes and timing for revising labels; and (iii) agree on existing stocks provisions to mitigate disruption on growers and other users. *Id*.

EPA career supervisory personnel were receptive to Gharda's June 7 commitment, reaching out the next day to ask "if Gharda is prepared to move forward with discussing voluntary use cancellations" and proposing a call with EPA legal counsel. *Id.* ¶ 25. By email dated June 8, 2021, EPA indicated that it was "considering the following dates for existing stocks:

- Technical grade active ingredient: Phase out most [1X] uses by the end of 2021; allow until the end of 2022 (12 to 18 months) for the remaining [1X] uses
- End-use products: 12 to 18 months from the technical registrants for sale/distribution of products
- End users, growers: Until exhausted"

Id. & Ex. D. Gharda responded to EPA's June 8 email proposing a meeting with its attorneys, with the expectation that the parties were close to reaching final agreement on terms and could begin work on modifying labels. *Id.* ¶ 26 & Ex. E.

Then, on June 14, 2021, EPA career supervisory personnel advised Gharda that Gharda's commitment regarding the "voluntary" cancellation of uses were not sufficient for EPA's "leadership," and asked Gharda to consider voluntarily cancelling yet additional uses, this time including the removal of some 10X uses, or face possible revocation of all tolerances. *Id.* ¶ 27.

EPA urged Gharda to agree to voluntarily cancel all but five to six of its most important crop uses. *Id*. This was the first time that EPA asked Gharda to consider voluntarily cancelling 10X crop uses. *Id*. EPA also said that its leadership had raised occupational exposure concerns, and asked that Gharda agree to eliminate the use of aerial application methods, even though these are not issues to be addressed under FQPA but are instead issues to be addressed in Registration Review under FIFRA's risk/benefit standard. *Id*. In subsequent calls, EPA also expressed concerns regarding ecological risks from chlorpyrifos, even though the ecological risk assessment for chlorpyrifos has yet to be completed. *Id*. EPA nevertheless continued to indicate openness to an extended phase-out period for any voluntarily cancelled uses. *Id*.

Gharda was confused, surprised, and disappointed at EPA's request that Gharda agree to voluntarily cancel 10X uses that EPA had confirmed, in a robust scientific assessment in its PID, would not exceed safe levels. *Id.* ¶ 28. Gharda was also concerned that EPA appeared to be relying on occupational and ecological concerns as the basis for its request, neither of which relate to the regulation of tolerances under the FFDCA. *Id*. Despite this dramatic and unexpected shift in the discussions, Gharda remained willing to work with EPA to try to meet its demands. *Id*. Gharda repeatedly urged EPA to ensure an orderly phase-out for manufacturers, distributors, growers, and others in the agricultural supply chain, as EPA's demand would eliminate nearly 80–85% of the U.S. market for chlorpyrifos. *Id.*

Gharda and EPA had a meeting on June 24, 2021 to further discuss terms. *Id.* ¶ 29. In a follow-up email dated June 24, 2021, approximately two months from the deadline for EPA to act in response to the Ninth Circuit order, ***EPA's Chemical Review Manager wrote Gharda*** "to confirm the uses that Gharda has agreed upon for retention following our discussions over the past few weeks and on our call this afternoon" and outlined the following terms:

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Cotton and strawberry will be phased out over two years (until 2023)
- Aerial application will be phased out over 2 years (until 2023)
- Provisions for existing stocks:
    - Technical products [with current labels] may be sold or distributed until 12/31/2021
    - End-use products [with current labels] may be sold or distributed until 12/31/2022

Id. & Ex. F.

In emails dated June 25, 2021, Gharda sought further clarification from EPA on some of the details of its June 25 proposal, including the details of various phase-out periods. *Id.* ¶ 30. In these emails, Gharda thanked EPA "for our good faith negotiations over the last few weeks" and said that it "looks forward to working with the Agency to finalize the above terms." *Id.* & Ex. G. EPA proposed a meeting with its Office of General Counsel. *Id.* It was Gharda's expectation that in involving legal counsel, the parties would be working to finalize a written agreement reflecting the agreed terms. *Id.*

At EPA's request, on July 2, 2021, Gharda had a further call with EPA career supervisory personnel, during which EPA pressed Gharda to agree to voluntarily cancel even more 10X crop uses because of demands from EPA's leadership. *Id.* ¶ 31. EPA also indicated that it would not be able to agree to an extended phase out period but that chlorpyrifos applications would need to cease after six months, instead of the phase-out periods that ***EPA had proposed*** one week earlier in its June 24 email. *Id.* EPA also raised concerns with air blast applications on orchard crops. *Id.* Gharda offered to provide data on mitigation measures that would address EPA's concerns regarding occupational exposure, but EPA said it would not consider mitigation data. *Id.* EPA asked Gharda to put forward its best, final proposal that EPA would take to its leadership. *Id.* Gharda was especially surprised and disappointed with this turn of events, as it in good faith

believed that EPA's June 24 email, *see id.* ¶ 29 & Ex. F, had set forth the final terms of crop use retention and voluntary cancellation. *Id.*

At EPA's request, Gharda had a call with EPA and its counsel on July 6, 2021. *Id.* ¶ 32. During the call EPA pressed Gharda to accept voluntary cancellation of all but three 10X uses and reiterated that it would be unable to allow use beyond six months from the effective date of a final rule. EPA explained that the six-month period was based on the World Trade Organization (WTO) Agreement on the Application of Sanitary and Phytosanitary measures, not because of a need for the orderly phase-out of chlorpyrifos inventories and existing stocks. *Id.* Gharda explained that six months would not be a meaningful time period, given that it would largely overlap with the off season for chlorpyrifos use and because its customers purchase product at least one to two years in advance of each growing season. *Id.* Following this call, Gharda followed up in writing to offer voluntary cancellation of additional 10X uses and eliminate aerial and air blast methods of application; Gharda urged EPA to extend the phase out periods for formulation, distribution, and use, to allow for an orderly exhaustion of inventories and to minimize potentially catastrophic economic losses to Gharda and others in the supply chain, at a minimum until July 2022 to cover part of the next growing season. *Id* & Ex. H. After this exchange, EPA indicated that it was "very close" to reaching final agreement with Gharda. *Id.*

At EPA's request, Gharda had a further call with EPA and its counsel on July 14, 2021, during which EPA indicated that Gharda's proposal was under review by EPA leadership but that EPA hoped to have a final response within a week. *Id.* ¶ 33. EPA indicated that it would likely need a voluntary cancellation letter from Gharda quickly, in order to be able to reference the voluntary cancellation in the published final rule. *Id.* During the call, EPA, for the first time, indicated that its leadership believed that import tolerances would also need to be voluntarily

cancelled. *Id*. EPA could not explain the basis for this last-minute request, given that import tolerances do not raise drinking water or occupational concerns, and given that the PID did not identify any dietary (non-drinking water) risks associated with chlorpyrifos use in the U.S or import tolerances, even with the retention of the 10X safety factor. *Id*. Nevertheless, believing it was very close to reaching final agreement with EPA and to avoid derailing months of negotiations, Gharda submitted a proposal to EPA for the cancellation of certain import tolerances. *Id.* & Ex. I. Gharda followed up asking EPA to consider its points concerning import tolerances, but stressed that it did not want the import tolerance issue to stand in the way of resolving voluntary cancellation of uses pursuant to the terms discussed, as summarized in Gharda's July 6 email. *Id.* & Ex. J. EPA responded stating that it appreciated Gharda's engagement on this challenging issue. *Id*.

3. *After Leading Gharda to Believe a Final Agreement Regarding Voluntarily Cancellation of Many Uses Was Imminent, EPA Abruptly Ceases Discussions and Announces It Is Revoking All Tolerances*

Following Gharda's July 14 submission and EPA's response, Gharda heard nothing further from EPA for weeks. *Id.* ¶ 34. Growing increasingly concerned as the court deadline for EPA to issue a final rule was approaching, Gharda requested a meeting with EPA leadership. *Id.* ¶ 35. After Gharda's repeated outreach, EPA finally allowed Gharda to have a twenty-five minute meeting with Assistant Administrator Freedhoff and others from EPA on August 16, 2021. *Id.* During the meeting, Gharda reiterated its commitment to voluntarily cancel uses as set forth above, urged EPA to make a decision consistent with science and law, and again stressed the major supply chain disruptions and catastrophic losses that would result from a revocation of tolerances with immediate effect. *Id*. EPA was silent during this meeting, indicating only that it was willing to "work collaboratively" with Gharda going forward. *Id*.

The next day after its meeting with EPA leadership, Gharda discovered a posting on EPA's website announcing the August 2021 revocation of all tolerances for chlorpyrifos, which Gharda also discovered was posted days **before** its meeting with EPA leadership. *Id.* ¶ 36 & Ex. L. When Gharda reached out to EPA about the posting, EPA apologized for the posting and immediately removed it, but confirmed that the final rule would be consistent with the website. *Id*. EPA indicated that there would be "elbow room" on timing of the final rule's implementation. *Id.*

C. EPA's Final Rule Revoking All Tolerances for Chlorpyrifos

EPA announced the Final Rule on August 18, 2021, which was published in the Federal Register on August 30, 2021. 86 Fed. Reg. 48,315. In the Final Rule, EPA stated that it is revoking all food use tolerances for chlorpyrifos. *Id.* at 48,317. EPA stated that, "[b]ased on the currently available data and taking into consideration the currently registered uses for chlorpyrifos," it is unable to make a safety finding under the FFDCA, even including an FQPA safety factor of 10X. *Id.* at 48,315, 48,317. EPA did not rely on any new data or scientific analyses in reaching this conclusion. In fact, the scientific analysis in the Final Rule is largely consistent with the Agency's scientific findings in the PID. Among other things, EPA continued to apply 10% RBC AChE as the regulatory endpoint for risk assessment, which it deemed "well-established." *Id.* at 48,317. Consistent with the PID, EPA stated that it "remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported" in epidemiology studies. *Id.* at 48,324.

As to the aggregate exposure assessment, EPA confirmed in the Final Rule, as it had found in the PID, that "exposures from food and non-occupational exposures individually or together do not exceed EPA's levels of concern." *Id.* at 48,333. EPA agreed in the Final Rule that it is only drinking water exposures, when combined with food and non-occupational

(residential) exposures, that create risks of concern. *Id.* As to drinking water, the Final Rule acknowledged EPA's findings in the PID that drinking water exposures do not exceed levels of concern when assuming use on only eleven high-benefit crops in select regions. *Id.* Nevertheless, and despite admitting that "there may be limited combinations of uses *that could be safe*," EPA claimed that because it is required to assess aggregate exposure taking into account all "currently registered uses" and based on the 2016 DWA, it could not find that aggregate exposures to chlorpyrifos are safe. *Id*. The Agency stated, with no further explanation, that it lacked "effective mitigation upon which to base a reduced aggregate exposure calculation." *Id.* The Final Rule stated that the tolerances would expire on February 28, 2022, six months from the date of publication, purportedly to comply with international trade obligations. *Id.* at 48,334.

EPA issued a press release in conjunction with the Final Rule. EPA, *EPA Takes Action to Address Risk from Chlorpyrifos and Protect Children's Health*, https://www.epa.gov/newsreleases/epa-takes-action-address-risk-chlorpyrifos-and-protect-childrens-health (Aug. 18, 2021). In the press release, EPA stated that the Final Rule would "help to ensure children, farmworkers, and all people are protected from the potentially dangerous consequences of this pesticide," and "follow[s] the science and put[s] health and safety first." *Id.*

After the Final Rule was announced, EPA held a public briefing session on the Rule. Seethapathi Decl. ¶ 38. EPA invited stakeholders to submit questions to EPA regarding about the Final Rule. *Id*.

Following EPA's public briefing, Gharda and others submitted questions to EPA, concerning the Final Rule's scope, applicability, timing for implementation, and harmonization

with FIFRA. *Id.* ¶ 39. Gharda specifically asked whether EPA would consider mitigation in light of Gharda's commitment to accept label modifications limiting use of chlorpyrifos to the select crop uses in select regions EPA determined were safe in the PID. *Id.* Among other questions, Gharda also asked whether EPA had reviewed or was willing to consider the 2020 Corteva drinking water study. *Id.*

On September 20, 2021, over a month after the Final Rule was announced, EPA posted responses to "Frequent Questions about the Chlorpyrifos 2021 Final Rule" ("FAQs") on its website,[1] and responded directly to Gharda's questions that were not addressed in the FAQs. *Id.* ¶ 40. EPA's responses did not appear to allow any "elbow room" or opportunities to "work collaboratively" on the Rule's timing and implementation, but instead directed interested parties to submit objections. *Id.* EPA also did not respond to Gharda's question concerning label modifications consistent with the Agency's safety finding, and indicated that "due to time constraints" it was unable "to conduct additional scientific analysis beyond what was already available at the time of the court ruling." *Id.*

VI. GHARDA'S OBJECTIONS

A. OBJECTION 1: EPA's Final Rule Revoking All Tolerances Is Arbitrary and Capricious Because it Ignores EPA's Own Safety Finding for Eleven Critical U.S. Crop Uses.

EPA's Final Rule revoked all tolerances because EPA claimed it could not make a safety finding for all currently registered uses. EPA arbitrarily disregarded its own, most conservative assessment in its PID and 2020 DWA, which provided a clear scientific basis for retention of tolerances for eleven critical crop uses. EPA stated unequivocally in the PID that limiting use to eleven high-benefit crop uses in select regions "***will not pose potential risks of concerns with an***

[1] https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule#question-2.

FQPA safety factor of 10X," meaning it had all of the science backing it needed to leave those uses in place. PID at 40 (emphasis added). EPA's Final Rule did not rely on any new scientific data or assessments that deviated from this finding.

EPA said that it was unable to rely on its PID and 2020 DWA because it is required to conduct an assessment that considers all "currently registered uses." *See* 86 Fed. Reg. at 48,333. However, there is nothing in the FFDCA or the Ninth Circuit order that requires EPA to make a safety finding that accounts for all currently approved uses. The FFDCA instructs that EPA consider "all *anticipated* dietary exposures and all other exposures for which there is *reliable information*." FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii) (emphasis added) (Determination of safety). This language is forward-looking; it is unreasonable to construe it to require EPA to assess only the uses that it previously approved. *See Kaseman v. District of Columbia*, 444 F.3d 637, 642 (D.C. Cir. 2006) (statutes should be interpreted to avoid untenable distinctions, unreasonable results, or unjust or absurd consequences). There is nothing prohibiting EPA from making a safety finding as to only a subset of uses in certain regions when it has "reliable information" at its disposal to do so. EPA's failure to acknowledge its authority to do so is particularly troubling when, as here, it has engaged in "good faith" negotiations with a registrant that is willing to accept a subset of critical crop uses.

EPA's construction would lead to the absurd result that the Agency could never modify tolerances to limit use of previously registered products based on new or updated scientific data. *See Kaseman*, 444 F.3d at 642. Indeed, EPA's Final Rule is directly at odds with the Ninth Circuit decision, which specifically acknowledged that the PID "propos[ed] to modify certain chlorpyrifos tolerances" and recognized that EPA could find, based on the PID, that "modified tolerances or registrations [are] safe." *LULAC*, 996 F.3d at 703.

Not only does EPA have the authority to modify tolerances and to take other regulatory action to conform to its safety finding, it routinely does so. Reiss Decl. ¶ 17. EPA regularly conducts risk assessments in which it determines that some uses but not others exceed the "risk cup" and requires appropriate relabeling and mitigation measures. *Id.* In fact "[t]his is fundamental to the Agency registration process." *Id.* For example, much like in the 2020 DWA, "EPA conducts an assessment that assumes a set of proposed uses" when it registers a new product. *Id.* This is consistent with the statutory directive that EPA consider "all anticipated exposures." *Id.; see* FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii). "Thus, there is no scientific reason why the 2020 DWA could not form the basis of a decision on the future of those 11 crops and only those 11 crops." *Id.*

Moreover, EPA has a guidance for conducting geographic-specific and regional drinking water assessments that EPA references in the Final Rule. 86 Fed. Reg. at 48,329 (citing https://www.epa.gov/sites/default/files/2020-09/documents/framework-conducting-pesticide-dw-sw.pdf) (Sept. 2020). EPA's guidance "outlines a tiered process for conducting drinking water assessments that relies on increasing refinement of the underlying assumptions in the assessment." Reiss Decl. ¶ 11. "The 2020 DWA applies the highest level of refinement (Tier 4) that is laid out in the EPA guidance" and reflects "the best available science for assessing drinking water risks." *Id.*

EPA states in the Final Rule that "without effective mitigation upon which to base a reduced aggregate exposure calculation, the products as currently registered present risks above the Agency's level of concern." *Id.* at 48,333. But the purpose of the 2020 DWA was to mitigate risks, and the PID provided recommended mitigation based on the 2020 DWA that EPA could have implemented to retain tolerances for a limited subset of uses in select regions. EPA

acknowledged this in the Final Rule. *See id.* at 48,322 (the PID proposal for the retention of 10X uses "was intended to offer stakeholders a way to mitigate the aggregate risk from chlorpyrifos"). It is unclear, and unexplained in the Final Rule, what additional mitigation the Agency believed it needed to determine that this limited combination of uses is safe. Gharda attempted to clarify this with the Agency in questions submitted to EPA after the Final Rule was announced at EPA's invitation, but EPA did not address this issue in its FAQs or responses to Gharda's questions. Seethapathi Decl. ¶ 39.

It is a foundational principle of administrative law that agencies must provide a reasoned explanation for departing from prior conclusions. *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009); *accord Motor Vehicle Mfrs. Ass'n of U.S. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983) (the agency must examine the relevant data and articulate a satisfactory explanation for its action). "Reasoned decision-making requires that when departing from precedents or practices, an agency must 'offer a reason to distinguish them or explain its apparent rejection of their approach.'" *Physicians for Soc. Resp. v. Wheeler*, 956 F.3d 634, 644 (D.C. Cir. 2020) (quoting Sw. *Airlines Co. v. FERC*, 926 F.3d 851, 856 (D.C. Cir. 2019); *see also Food Mktg. Inst. v. ICC*, 587 F.2d 1285, 1290 (D. C. Cir. 1978) (greater scrutiny applies to agency actions departing from prior norms and "it is at least incumbent upon the agency carefully to spell out the bases of its decision when departing from prior norms"). An agency may not "gloss[] over or swerve[] from prior precedents without discussion." *Sw. Ailines Co.*, 926 F.3d at 856 (citing *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 852 (D.C. Cir. 1970). Equally clear is the requirement that federal agencies act in a consistent, evenhanded manner. *See Sharron Motor Lines, Inc. v. United States*, 633 F.2d 1115, 1116 (5th Cir. 1981);

see also Powell v. United States, 945 F.2d 374, 377 (11th Cir. 1991) (recognizing "a claim for administrative inconsistency").

Here, EPA has arbitrarily and summarily cast aside its thorough and well-reasoned scientific assessments supporting a safety finding for a subset of critical crop uses without any logical explanation. This is precisely the type of agency action held arbitrary and capricious by reviewing courts. *See, e.g., Chlorine Chemistry Council v. EPA*, 206 F.3d 1286, 1290–91 (D.C. Cir. 2000) (vacating EPA rule that "openly overrode" its own science). EPA's abandonment of its scientific findings is especially troubling given that Gharda and other members of the regulated community rely on the Agency's assessments and trust and expect that EPA will make decisions that are rooted in science. *See Encino Motorcars, LLC v. Navarro*, 579 U.S. 211 (2016) (agency reversal of prior policy without a reasoned explanation was arbitrary and capricious, particularly where longstanding policy engenders reliance interests that must be taken into account) (citing *Fox Television Stations, Inc.*, 566 U.S. 502). The law is clear that EPA cannot regulate in this manner.

B. OBJECTION 2: EPA's Final Rule Is Arbitrary and Capricious Because it Disregarded a Commitment from Gharda to Modify its Registration In Accordance with the Agency's Safety Finding.

In addition to ignoring its own safety finding, EPA's Final Rule disregarded a written commitment from Gharda to voluntarily cancel the uses identified in the PID as the 1X uses, consistent with the Agency's safety finding in the PID. Gharda submitted this proposal to EPA nearly two months ahead of the Agency's deadline to act in response to the Court order, and was standing by to discuss the substance of Gharda's voluntary cancellation letter and necessary label modifications with EPA when the Agency abruptly and inexplicably withdrew from discussions. Seethapathi Decl. ¶¶ 24–34. EPA plainly had at its disposal the "effective mitigation" necessary

to modify tolerances based on its safety finding for the 10X uses. Its decision to instead revoke all tolerances, without any explanation, was arbitrary and capricious.

C. OBJECTION 3: EPA Acted Arbitrarily and Capriciously and in Bad Faith in Negotiating a Voluntary Cancellation with Gharda—During which Gharda Met Each of EPA's Continually Increasing and Unjustified Demands—Only to Then Abruptly and Inexplicably Revoke All Tolerances.

All currently approved uses of chlorpyrifos are safe, based on the weight of the scientific evidence, and Gharda disagrees with EPA's application of an FQPA 10X safety factor to address "uncertainties" in the scientific literature concerning neurodevelopmental effects. *See* Gharda Comments on PID, EPA-HQ-OPP-2008-0850-0999. Nevertheless, at EPA's request that Gharda entertain an agreement to voluntarily cancel certain currently approved uses of chlorpyrifos, and in an effort to cooperate with the Agency, Gharda spent months working with EPA to reach mutually agreeable terms. Seethapathi Decl. ¶¶ 21–34. Gharda poured enormous time and resources into these discussions. *See id.*

EPA initially focused these discussions on cancellation of the uses identified in the PID as 1X crop uses. *Id.* ¶¶ 21–26. In an effort to cooperate and given the Agency's timing concerns, Gharda ultimately agreed, even though such a reduction in uses would eliminate a substantial portion of its U.S. chlorpyrifos business. *Id.* Over a period of just a few weeks, EPA continually expanded its requests of Gharda to include cancellation of some 10X crop uses, then application methods, and later import tolerances—all without any scientific or legal basis. *Id.* ¶¶ 27–33. At the same time, EPA refused to consider Gharda's science-based mitigation proposals. *See id.* ¶ 31.

At every stage of these discussions, Gharda stressed to EPA the critical importance of reasonable phase-out and existing stocks periods, to avoid massive supply chain disruption and to minimize harm to growers. *Id.* ¶¶ 21, 23–24, 28. Until near the very end of discussions, EPA

was receptive to these concerns, even proposing phase-out periods of 12–18 months for formulators and distributors and until exhaustion for growers. *Id*. ¶¶ 25, 29. EPA then retreated from these terms, too, even for the 10X crop uses it had found safe. *Id*. ¶¶ 31.

While Gharda was disappointed that EPA repeatedly sought to eliminate additional uses, impose additional label restrictions, and shorten the period for implementation, Gharda met each of EPA's requests cooperatively and fairly. *Id*. ¶¶ 21–33. Believing that it was close to reaching agreement with EPA and given the court-imposed time constraints, Gharda eventually agreed to accept, *in writing*, the voluntary cancellation of most uses, with additional label restrictions. *Id*. As requested by EPA, Gharda stood by, waiting for EPA's request that Gharda submit a formal letter seeking voluntary cancellation of uses. EPA then abruptly and inexplicably ceased discussions with Gharda, until the Final Rule was announced. *Id*.

The Agency's conduct and processes leading up to the Final Rule were fundamentally unfair. Gharda went above and beyond to meet EPA's continually increasing demands, and believed it was dealing with the Agency in good faith. Then, the Agency changed course and announced the Final Rule, with no notice to Gharda or explanation. Beyond lacking a scientific basis, the last-minute turn of events was a surprise to Gharda and other members of the regulated community, and departed from months of discussions in which EPA led Gharda to believe that several key crop uses would survive and Gharda, in turn, acted in reliance on those representations. Even EPA's final pre-final rule meeting with Gharda was stained by the discovery that EPA had already posted on its website *before the meeting* its intentions with respect to the final rule. Despite EPA's claimed interest in working with Gharda "collaboratively," EPA has shown no willingness to do so since the Final Rule was announced, nor any flexibility in the Rule's implementation, notwithstanding the chaos it has caused in the

agricultural supply chain. This is not how a U.S. federal agency should deal with regulated parties.

It appears clear that EPA's Final Rule was not driven by science or fair dealing with the regulated community. This is evident not only from the constantly moving goalposts in Gharda's discussions with EPA leading up to the Rule's announcement, which were not rooted in science, but also from EPA's prejudicial and misleading public messaging around the Rule, which cited reasons for revocation that are unsupported by science and inconsistent with the Rule itself. *See* Seethapathi Decl. ¶ 45.

In short, EPA's conduct and regulatory process demonstrate bad faith, A showing of bad faith by an agency undermines the reasonableness of the agency's decisionmaking and supports a finding that its actions are arbitrary and capricious. *See Dallas Safari Club v. Bernhardt*, 518 F. Supp. 3d 535, 542–43 (D.D.C. 2021) (when a party challenges agency action as arbitrary and capricious, the reasonableness of agency action is judged "in accordance with its stated reasons . . . *unless there is a showing of bad faith or improper behavior*") (emphasis added) (citation omitted); *Ctr. for Biological Diversity v. Trump*, 453 F. Supp. 3d 11, 34 (D.D.C. 2020) ("a strong showing of bad faith or improper behavior . . . suggests arbitrary and capricious decisionmaking") (citations omitted).

D. OBJECTION 4: EPA's Final Rule is Arbitrary and Capricious Because the Agency Failed to Give Adequate Consideration to Relevant Scientific Data and Information.

EPA issued the Final Rule without considering important scientific data. This includes comments and other submissions Gharda supported through an industry task force that highlighted numerous flaws in the Agency's 2016 DWA. *See* DAS Comments on 2016 Notice of Data Availability, Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos, at 5EPA-HQ-OPP-2015-0653-0651 (Jan. 17, 2017) (commenting

on 2016 DWA as an overly conservative, screening-level estimate that far over-estimates real world exposures and ignores science-based refinements submitted by the registrant); *see also* DAS Response to Objections to EPA's Denial of Petition to Revoke Tolerances and Cancel Registrations for Chlorpyrifos (and supporting Declarations), EPA-HQ-OPP-2007-1005-0526) (Aug. 27, 2018) (challenging objections asserting drinking water risk concerns as based on the incomplete and unrefined 2016 DWA); *see also* Reiss Decl. ¶ 13 (addressing "significant limitations" in 2016 DWA). EPA's reliance on the 2016 DWA to justify revoking tolerances—without considering these comments on the 2016 DWA and in disregard of EPA's far more robust and highly refined 2020 DWA—is arbitrary and capricious. *See Conner v. Burford*, 848 F.2d 1441, 1453–54 (9th Cir. 1988) (Fish and Wildlife Service acted arbitrarily and capriciously in failing to prepare biological opinion based on best scientific data available).

EPA also failed to review a Corteva drinking water study submitted to EPA in December 2020, around the time the PID was released, which analyzed cholinesterase inhibition in rats following exposure to chlorpyrifos oxon. *See A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days*, MRID 51392601. EPA was consulted on the design of the study and provided feedback to Corteva, and the interim results were presented to EPA in August 2020, well before the issuance of the PID. Reiss Decl. ¶ 23. The study found "(a) no detectable circulating chlorpyrifos oxon in blood, (b) no statistically significant AChE inhibition in either RBC or brain, and (c) an absence of clinical signs of toxicity or markers of exposure." *Id.* ¶ 27. This study nullified EPA's assumption in the 2020 DWA "that chlorpyrifos oxon is more toxic than the parent chlorpyrifos for drinking water exposure purposes." *Id.* ¶ 29. The study demonstrates that "drinking water risks associated with the oxon are not a risk concern for any agricultural

uses of chlorpyrifos and should not be part of the EPA's aggregate risk assessment or serve as a basis for limiting uses of chlorpyrifos." *Id.* ¶ 30.

Gharda urged EPA to consider this critical study, both in its comments on the PID and during discussions with EPA concerning a potential voluntary cancellation of uses. *See* Gharda Comments on PID, EPA-HQ-OPP-2008-0850-0999; Seethapathi Decl. Ex. A. Gharda also specifically asked EPA in questions submitted in response to the Final Rule whether EPA had considered the study or was willing to do so in the near term. *Id.* ¶ 39. In response, EPA stated that it "has the Corteva drinking water study in house for review" but that "[d]ue to time constraints, EPA was not able to conduct additional scientific analysis beyond what was already available at the time of the court ruling." Seethapathi Decl. Ex. K.

EPA's position is untenable. To be sure, the Ninth Circuit ordered EPA to revoke or modify tolerances within sixty days and found that it would not "be reasonable to remand for further factfinding after thirteen years of interminable delay." *LULAC*, 996 F.3d at 702. But the Ninth Circuit decision did not give EPA license to ignore highly relevant scientific data invested in by the registrants that EPA has *had at its disposal* for months leading up to the court decision and that EPA will have had for over a year by the time the Final Rule takes effect. Indeed, the Ninth Circuit decision specifically contemplated that EPA's "further research" could provide the basis for "modif[ying] chlorpyrifos registrations rather than cancelling them." *LULAC*, 996 F.3d at 703. Nor does the decision justify EPA's refusal to even entertain science-based mitigation proposals Gharda offered to put forward in response to EPA's occupational risk concerns, concerns which although irrelevant to food tolerances plainly appear to have driven EPA's revocation decision. *See* https://www.epa.gov/newsreleases/epa-takes-action-address-risk-chlorpyrifos-and-protect-childrens-health (EPA press release stating that Final Rule would

protect farmworkers from "potentially dangerous consequences of this pesticide"). The drinking water study and other data Gharda was prepared to submit should not have required significant time or effort for EPA to review. *See* Reiss Decl. ¶ 23 (explaining that the 2020 Corteva study "is not onerous to review or interpret and EPA could have done so before the issuance of the PID and certainly well before the issuance of the Final Rule").[2]

EPA has a statutory duty to make decisions based on valid, complete, and reliable data. FFDCA § 408a(b)(2)(D), 21 U.S.C. § 346a(b)(2)(D)(i). The need for EPA to carefully consider all relevant data at its disposal is all the more important given the significant due process issues at stake, and the disruption its draconian revocation action has caused and will continue to cause on the agricultural marketplace. *See infra* at 35–36; Seethapathi Decl. ¶¶ 41–49. By pressing ahead with its overly broad revocation order while ignoring relevant data under the guise of court-imposed time pressures, the Agency's decision rests on incomplete data and is arbitrary and capricious. *State Farm Mut.*, 463 U.S. at 43 (agency's failure to examine all relevant data is arbitrary and capricious); *see also Love v. Thomas*, 858 F.2d 1347, 1358–59 (9th Cir. 1988) (reversing EPA suspension order based in part on agency's reliance on insufficient data); *Greenpeace v. Nat'l Marine Fisheries Serv.*, 80 F. Supp. 2d 1137, 1150 (W.D. Wash. 2000) (agency acted arbitrarily and capriciously by relying on incomplete information and ignoring relevant data).

[2] Gharda respectfully submits that EPA has all of the scientific data at its disposal to find that chlorpyrifos oxon is not relevant to EPA's aggregate exposure assessment under the FFDCA. To the extent that EPA believes that a fact issue is presented by this data, Gharda respectfully requests a hearing. *See* FFDCA § 408(g)(2)(B), 21 U.S.C. § 346a(g)(2)(B).

E. OBJECTION 5: EPA Failed to Afford Gharda and Other Stakeholders Adequate Procedural Due Process.

A pesticide registration is a recognized property right under FIFRA. *See Reckitt Benckiser, Inc.*, 762 F. Supp. 2d at 45 ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute."); *Mem. & Order, Pesticide Action Network N. Am.*, No. C 08-1814, at 4 (N.D. Cal. July 8, 2008), ECF No. 43 ("The registrations involved here are essentially government licenses to produce, distribute and sell pesticides . . . [and] therefore constitute property[.]"). As such, it cannot be taken away without due process of law. *See Indus. Safety Equip. Ass'n*, 656 F. Supp. at 856 ("It is well settled that an agency license can create a protectible [sic] property interest, such that it cannot be revoked without due process of law.").

EPA's revocation of tolerances based on alleged drinking water concerns, without responding to comments and critical scientific data submitted by the registrants that directly address those concerns, raises significant due process issues. Through an industry task force, Gharda has supported the submission of detailed comments on and proposed science-based refinements to the Agency's 2016 DWA. EPA has had these materials since as early as January 2017 but has never responded to them, despite committing to do so. Indeed, in July 2019 EPA acknowledged that "certain uses, application rates, and practices" described in the chlorpyrifos labels overestimate drinking water exposure, and stated that it had requested additional information from the registrants to confirm the accuracy of these assumptions, which it would then incorporate into its Proposed Interim Decision. *See, e.g., Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order*, 84 Fed Reg. 35,555, 35,566 (July 24, 2019). EPA noted for example that it was pursuing surface water monitoring data that would allow it to "confidently estimate pesticide concentrations in surface water that may be sourced by

community water systems." *Id.* EPA's failure to review scientific data and comments provided by the registrants is troubling given that EPA revoked tolerances in the Final Rule *based on the 2016 DWA*, without any reasoned explanation or scientific basis for abandoning its far more robust, highly refined 2020 DWA.

EPA has also refused to consider the Corteva drinking water study submitted in December 2020 (and in draft form months earlier), which nullifies EPA's assumptions concerning drinking water risks from chlorpyrifos oxon. Reiss Decl. ¶¶ 23–30. EPA has also failed to review and respond to comments on the PID and underlying assessments submitted by Gharda and other stakeholders months before the Ninth Circuit's decision. These comments urged EPA to review and act on the Corteva drinking water study and challenged EPA's application of an FQPA 10X safety factor to address "uncertainties" in unreliable epidemiology data. By not responding to these comments and other submissions, which challenge directly EPA's rationale for revocation of all tolerances, EPA has denied Gharda and other interested parties meaningful notice and comment.

EPA must correct its due process violations and commit to a meaningful, thorough review of objections. It must also commit to reviewing the relevant scientific data and science-based comments bearing on the drinking water issues it has had at its disposal for months, years in some instances, and to modifying its revocation order as appropriate, before the Final Rule and tolerance expiration take effect.

F. OBJECTION 6: The Final Rule Infringes the Substantive Due Process Rights of Gharda and other Affected Parties.

There is a fundamental requirement under the Constitution that substantive standards of justice must be applied to assure that there is no deprivation of life, liberty, or property rights. This "substantive due process" doctrine forbids a regulatory body from taking an action that is

substantively so unfair that fundamental rights are abridged, even if proper procedures are followed.

As the Supreme Court stated in *Nebbia v. New York*, 291 U.S. 502, 525 (1934), "the guaranty of due process … demands … that the law shall not be unreasonable, arbitrary or capricious." The law is clear that "the possibility of arbitrary, undocumented action will not be tolerated when protected [property] rights are at stake." *Roane v. Callisburg Indep. Sch. Dist.*, 511 F.2d 633, 639 (5th Cir. 1975); *see also United States v. Carolene Prods. Co.*, 304 U.S. 144, 152–53 &n.4 (1938); *Anthony v. Franklin Cnty.*, 799 F.2d 681, 684 (11th Cir. 1986). Gharda and other registrants affected by the Final Rule have a fundamental property right in their registrations, which is protected by the substantive due process doctrine. The economic value of a registration for food use crops is dependent on having the appropriate tolerances in place. The Agency's action in revoking all tolerances without a reasoned explanation or valid scientific basis, and in disregard of scientific data that support the retention of tolerances, has improperly deprived Gharda of the economic value of its registration for chlorpyrifos. This action constitutes a clear violation of Gharda's substantive due process rights, and has unfairly and arbitrarily deprived Gharda of fundamental property rights.

G. OBJECTION 7: EPA Has Acted Arbitrarily and Capriciously in Imposing an Unreasonably Short Implementation Timeframe That Will Cause Significant Harm to Gharda and Other Affected Parties.

EPA's Final Rule proposes to take effect six months from the date of its publication on August 30, 2021, or on February 28, 2022. 86 Fed. Reg. 48,334. The 2021 growing season has essentially ended, and chlorpyrifos would not be used until the next growing season beginning approximately in April 2022. Seethapathi Decl. ¶ 40. Thus, even if the Final Rule had a valid scientific justification, the six-month period imposed for the Rule's implementation is effectively

meaningless and allows no time for Gharda, distributors, and growers to phase out inventories and exhaust existing stores of chlorpyrifos. *Id.*

EPA has claimed in discussions with Gharda and in the Final Rule that the six-month period is necessary because the WTO Agreement on the Application of Sanitary and Phytosanitary Measures requires members to allow a "reasonable interval" between publication of a sanitary or phytosanitary regulation and its effective date, to allow time for exporting members, particularly developing countries, to adapt their products and production methods to the regulation. *Id.* ¶ 32; 86 Fed. Reg. 48,334. But the WTO has interpreted "reasonable interval" to mean a period of *not less than* six months." 86 Fed. Reg. 48,334 (emphasis added). The six-month requirement under the WTO agreement is thus a floor, not a ceiling as EPA has implied.

EPA's imposition of a six-month, off-season period for the Final Rule to take effect will result in extraordinary economic and other harms to Gharda, its distributors, and the end users of its products. Seethapathi Decl. ¶¶ 41–49. With Corteva's exit from the U.S. market for chlorpyrifos, Gharda increased production in order to meet customer demand and is now the primary supplier of chlorpyrifos for agricultural use in the U.S. *Id.* ¶¶ 10, 42. As a result, Gharda has a significant volume of raw materials and U.S. labeled product in inventory. *Id.* ¶ 42. If Gharda is unable to formulate, sell, and distribute these products for use in the 2022 growing season and beyond, Gharda will suffer Redacted - CBI economic losses, to say nothing of the nearly Redacted - CBI loss in its investment in chlorpyrifos and lost future sales of chlorpyrifos products in the U.S. of approximately Redacted - CBI annually. *Id.*

The short period for implementation has also strained Gharda's relationships with its customers, who distribute its products to suppliers and end users. *Id.* ¶ 44. In the months

leading up to the Final Rule, Gharda assured its customers that it was working cooperatively with EPA to reach an agreement that would allow for key agricultural uses to continue, consistent with EPA's safety finding in the PID. *Id.* EPA's abrupt departure from the negotiations and its own scientific findings has cast doubt on Gharda's credibility and resulted in a loss of customer goodwill. *Id.* ¶¶ 43–44.

Losses from an effectively immediate removal of chlorpyrifos from the U.S. market would not be borne by Gharda alone. *Id.* ¶ 47. It will also cause significant financial hardship to distributors and growers who invested substantial sums in reliance on the registration in products they are no longer able to sell or use. *Id.* Distributors face particularly dire economic consequences. Most distributors purchase products from Gharda at least a year in advance, and as a result have significant product on hand in order to meet market needs and often fluctuating demand by U.S. growers. *Id.* Gharda has been informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately [redacted], for which there will no longer be a viable market if the Final Rule takes effect. *Id.* Growers, for their part, not only face a lost investment in unusable product but also must find alternative, sometimes more expensive alternative products or risk significant crop losses. *Id.* In total, the volume of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers is estimated to be valued at Redacted - CBI. *Id.* Finally, commodity traders and other holders of food and feed with detectable chlorpyrifos residues face significant uncertainty, as it may be practically impossible to demonstrate that the residues result from a lawful application, particularly in the case of finished food and feed product with extended shelf lives. *Id.* ¶ 48. This confusion could result in the unnecessary waste of otherwise safe and nutritious food and

feed. *Id.* In short, EPA's Final Rule will impose damage and harm throughout the agricultural value chain and an already fragile economy.

EPA was well aware of these impacts leading up to the Final Rule, and even signaled in discussions following the Final Rule's announcement that there was "elbow room" on timing for the Rule's implementation. *Id.* ¶ 36. EPA has since refused to engage with Gharda and other affected parties on these issues, outside of a formal objections process. *Id.* ¶ 40. EPA's unwillingness to allow any meaningful period for an orderly phase-out of chlorpyrifos products is unfounded and arbitrary and capricious, particularly in the case of the 10X crop uses that EPA found safe under the PID. At a minimum, EPA should revise the Final Rule to allow for a gradual, multi-year phase-out of crop uses, to mitigate significant economic harm to Gharda and others in the agricultural supply chain and to allow growers time to transition to other products.

H. OBJECTION 8: EPA's Failure to Harmonize its Revocation Decision with FIFRA Is Arbitrary and Capricious.

EPA has also failed to harmonize its Final Rule revoking tolerances with FIFRA, including by following appropriate cancellation procedures and implementing provisions for existing stocks, as it is required to do by statute. The FFDCA contemplates that EPA will coordinate any necessary tolerances revocations with the associated registration cancellations under FIFRA. *See* FFDCA § 408(l)(1), 21 U.S.C. §346a(l)(1) ("in issuing a final rule under this subsection that . . . revokes a tolerance . . . for a pesticide chemical residue in or on food, the Administrator shall coordinate such action with any related necessary action under [FIFRA]"). Even the Ninth Circuit order in *LULAC* expressly directed EPA, in issuing a final rule modifying or revoking tolerances, "to correspondingly modify or cancel related FIFRA registrations for food use in a timely fashion consistent with [its safety finding]." *LULAC*, 996 F.3d at 678.

The Final Rule is silent on any corresponding action under FIFRA. While EPA has said in its FAQs on the Final Rule that it "intends to cancel registered food uses of chlorpyrifos associated with the revoked tolerances under FIFRA, as appropriate,"[3] EPA has provided no explanation for how or when it will coordinate its revocation action with cancellation procedures under FIFRA. These include issuing a notice informing the registrant and the public of the cancellation, and sixty days prior to that notice, providing a copy of the intended notice to the Secretary of Agriculture, along with an analysis of the impact of the proposed cancellation on the agricultural economy. *See* 7 U.S.C. § 136d(b). EPA must also convene an SAP to provide comments to the Agency on "the impact on health and the environment" of proposed cancellation actions, *id*. § 136w(d), and publish in the Federal Register its analysis of any impacts on the agricultural economy, including impacts on production, prices of agricultural commodities, and retail food prices. *Id.* § 136d(b).

Given the exceedingly short time period for the Final Rule to take effect, it appears clear that any coordinated cancellation action under FIFRA will be *pro forma* at best, and will not provide appropriate due process to regulated parties or fully take into account or adequately notify the public of the significant impacts of cancellation on the agricultural economy. This includes economic harms to growers who rely on chlorpyrifos to meet their pest management needs and who will be forced as a result of the Final Rule to resort to less effective and/or more costly alternative products.

In addition to abridging cancellation procedures under FIFRA, the Final Rule is silent on provisions for existing stocks. In the FAQs accompanying the Final Rule, EPA stated that

[3] https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule#question-2.

because it "has not cancelled any chlorpyrifos products as a result of the final tolerance rule," "there are no existing stocks at this time."[4] In reality, however, there significant volumes of chlorpyrifos technical and end-use products currently log-jammed in the U.S. agricultural supply chain, and no guidance from EPA on how to responsibly handle them once the Final Rule takes effect. Without an existing stocks order, stores of chlorpyrifos products that remain in the supply chain could be used without regard to the product label, with potentially negative impacts on health and the environment, and EPA would be without authority to stop it. This is not what Congress intended. EPA has a statutory mandate under FIFRA to ensure the safe, lawful, and orderly phase-out of these products that it has not fulfilled in issuing the Final Rule.

Indeed, in enacting and amending FIFRA, Congress made clear its intent that EPA oversee a comprehensive regime for the regulation of pesticides in order to prevent unreasonable adverse effects on human health and the environment. *See Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 991–92 (1984). Thus, Congress vested EPA with authority over the sale, distribution, and use of pesticide products at all stages of the product life cycle, including the authority to provide—and enforce—an orderly process for their disposal. 7 U.S.C. § 136d. Specifically, FIFRA Section 6 empowers EPA to cancel the registration of an existing pesticide in certain circumstances, or to suspend the registration of a pesticide to prevent an imminent hazard. FIFRA § 6(a), (b); 7.U.S.C. § 136d(a), (b). Importantly, Section 6 also authorizes EPA to concomitantly enter an "existing stocks" order, in which EPA may "permit the continued sale and use of existing stocks of a pesticide whose registration is suspended or cancelled under [FIFRA Sections 6, 3, or 4], to such extent, under such conditions, and for such uses as the

[4] https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule.

Administrator determines that such sale or use is not inconsistent with the purposes of this subchapter." FIFRA § 6(a)(1); 7 U.S.C. § 136d(a)(1).

In the 1980s, Congress became increasingly concerned with EPA's ability to satisfactorily deal with potential adverse effects resulting from the storage, disposal, and transportation of pesticides whose registrations had been cancelled or suspended. *See, e.g.*, Hearing of the Environment, Energy and Natural Resources Subcommittee, Committee on Government Operations, 100th Cong. 1st Sess. (July 9, 1987) (citing cancellations of registrations for ethylene dibromide (EDB), 2,4,5-T, silvex, and dinoseb). As initially conceived, EPA had the authority and financial responsibility to accept suspended or canceled pesticides and dispose of them at government expense. Congress added several key provisions to FIFRA in 1988 to expand EPA's authority to oversee the sale, distribution, and use of pesticides whose registrations have been terminated by some means, including by authorizing EPA to take enforcement action against violations of storage, disposal, and transportation requirements. FIFRA Amendments of 1988, Pub. L. No. 100-532, 102 Stat. 2654; *see also* H.R. Rep. No. 100-939 (1988) (to accompany S. 659). Specifically, Congress added (i) FIFRA Section 19, which makes clear that existing stocks orders issued "under [Section 6]" may include "requirements and procedures" governing disposal, 7 U.S.C. § 136q(a)(2), and (ii) FIFRA Section 12(a)(2)(k), which authorized EPA to take enforcement action against violations of existing stocks orders under FIFRA Section 12, 7 U.S.C. § 136j(a)(2)(K). These provisions fill critical gaps in areas where EPA's authority over newly unregistered pesticides had been lacking or unclear.

EPA's authority to address existing stocks of pesticides for which registrations have been cancelled is critical because FIFRA prohibits the *distribution or sale* of an unregistered pesticide

but does not prohibit its *use*. FIFRA § 3(a); 7 U.S.C. § 136a(a). In fact, Congress omitted reference to "use" in the first sentence of Section 3(a) (making it unlawful to "distribute or sell" an unregistered pesticide) while including "use" in the second sentence (granting EPA authority to regulate "use" of unregistered pesticides in order to prevent unreasonable adverse effects):

> Except as provided by this subchapter, no person in any State may *distribute or sell* to any person any pesticide that is not registered under this subchapter. To the extent necessary to prevent unreasonable adverse effects on the environment, the Administrator may by regulation limit the *distribution, sale, or use* in any State of any pesticide that is not registered under this subchapter and that is not the subject of an experimental use permit under section 136c of this title or an emergency exemption under section 136p of this title.

Id. (emphasis added); *cf. S. Coast Air Quality Mgmt. Dist. v. EPA*, 472 F.3d 882, 894 (D.C. Cir. 2006) (Congress's inclusion of particular language in one section of a statute but omission of it in another is presumed to be intentional). FIFRA's enforcement provisions reinforce that use of unregistered pesticides is not unlawful: Section 12(a)(1) prohibits only the distribution and sale of unregistered products (not their use), and Section 12(a)(2)(g) prohibits only the "use" of a "registered pesticide" in a manner inconsistent with its labeling. 7 U.S.C. § 136j(a)(1), (a)(2)(G).

This framework presents several challenges in cases where previously registered products are rendered unregistered, including as a result of revoked tolerances.[5] Without an existing stocks order, end users of newly unregistered products would be free to use remaining stocks inconsistently with restrictions on the product label (which in the case of an unregistered pesticide is no longer enforceable). And because under FIFRA no party may "distribute or sell"—which includes "ship," "deliver for shipment," or "receive"—unregistered pesticides, *id*. § 136(gg), end users and others wishing to return existing stocks to the manufacturers or pursue other safe disposal options would be in violation of FIFRA. A comprehensive, enforceable order

[5] Although EPA has not yet issued the requisite cancellation notices, the term "unregistered" is applicable here in light of the practical effect of EPA's tolerance revocation actions.

on existing stocks thus ensures that post-termination use, sale, or distribution of newly unregistered products are within the scope of EPA's enforcement authority and that EPA is able to mitigate potential effects on human health and the environment.

Here, EPA issued the Final Rule revoking all tolerances, and acknowledged that it will be a violation of FIFRA to sell and distribute chlorpyrifos products labeled for use on food crops when the Final Rule takes effect, yet EPA disregarded its authority under FIFRA to oversee the orderly phase-out of existing stocks. As a result, there is considerable confusion as to how to handle significant stores of chlorpyrifos products that exist in the supply chain. Seethapathi Decl. ¶ 47 (explaining how distributors purchase at least a year in advance). Absent some action from EPA to address existing stocks, the agency would be powerless to prevent the use of chlorpyrifos products not in accordance with the previously operative label restrictions, which has the potential to adversely impact the environment. 7 U.S.C. § 136j(a)(1), (a)(2)(G).

In short, in taking action to revoke all tolerances without an existing stocks order, EPA has abdicated its duty under FIFRA to oversee the safe, orderly, and lawful disposal of the products that will be rendered essentially unregistered as a result of the Final Rule. A product that has been extensively used in the United States under EPA's oversight for decades cannot simply become, overnight, a harmful product undeserving of existing stocks provisions. If EPA persists in implementing the flawed Final Rule, it must *at a minimum* extend the expiration of tolerances coextensive with an appropriate existing stocks order, to provide guidance and clarity to affected parties and to mitigate risks to health and the environment.

I. OBJECTION 9: EPA's Revocation of Import Tolerances Lacks a Scientific Basis and Is Therefore Arbitrary and Capricious.

There is no scientific basis for EPA's revocation of import tolerances. Import tolerances regulate pesticide residues in or on foods that are imported into the United States; the pesticide

uses associated with these tolerances occur in other countries. Thus, dietary (food) exposures from imported foods are the only relevant exposures for purposes of EPA's FFDCA risk determination; drinking water is not a component of the FFDCA risk determination. EPA's PID and 2020 RHHRA did not identify any dietary risks associated with chlorpyrifos use in the United States or with import tolerances, even with the retention of the FQPA 10X safety factor. 2020 RHHRA at 12; PID at 14, 18; Reiss Decl. ¶ 31. EPA's dietary risk assessment includes domestic and imported food; if only imported food were considered, any potential risks would be even lower. Gharda raised all of these issues with EPA in discussions leading up to the Final Rule, and yet EPA's Final Rule revoked all tolerances. Seethapathi Decl. ¶ 33. EPA's blanket revocation of import tolerances it has acknowledged are safe is arbitrary and capricious. Reiss Decl. ¶ 31; *see also Nat'l Corn Growers Ass'n v. EPA.*, 613 F.3d 266, 275 (D.C. Cir. 2010) (vacating as arbitrary and capricious EPA decision to revoke import tolerances for carbofuran "because the EPA itself considered them safe").

EPA's guidance on pesticide import tolerances makes clear that where tolerances are revoked for reasons other than due to dietary risk concerns, "use in other countries may continue" and "EPA will consider requests (normally by petition) to modify or maintain a tolerance as an import tolerance." *Pesticides; Guidance on Import Tolerances & Residue Data for Imported Food*, 65 Fed. Reg. 35,069, 35,072 (June 1, 2000). Import tolerances "may be maintained provided that there is a need for the tolerance because the pesticide is used outside of the U.S. on commodities intended for the U.S. market" and provided the tolerance "meets the food safety requirements of FFDCA." *Id.* Gharda accordingly requests that EPA allow for the retention of all import tolerances for chlorpyrifos, consistent with the Agency's safety finding. Any refusal by EPA to allow for the retention of import tolerances it has conceded are safe

would be arbitrary and capricious and an improper attempt to influence the regulatory policy of foreign countries. *Id.* ("The Agency has no authority to regulate pesticide use in other countries."); *see also EPA Order Denying ABC's Petition to Revoke Import Tolerances for Various Pesticides*, 76 Fed. Reg. 49,318 (Aug. 10, 2011) (denying petition to revoke import tolerances based on alleged environmental risks in other countries as outside EPA's authority under the FFDCA).

J. OBJECTION 10: EPA's Final Rule Failed to Comply with Interagency Review Processes.

Under Executive Order 12866, federal agencies must submit "significant regulatory actions" for review to the Office of Management and Budget's Office of Information and Regulatory Affairs ("OIRA"). "Significant regulatory actions" include "any regulatory action that is likely to result in a rule that may … [h]ave an annual effect on the economy of $100 million or more" or "adversely affect in a material way the economy, a sector of the economy, productivity, competition, jobs, the environment, public health or safety, or State, local, or tribal governments or communities." *Id.*

Gharda objects to EPA's determination that the Final Rule is exempt from OIRA review. OMB has clarified in guidance that actions that make existing tolerances more stringent are not exempt from OIRA review.[6] This unquestionably includes tolerance revocations.

Moreover, the Final Rule's impact on the economy will easily exceed $100 million and/or materially affect the agricultural economy, given the devastating harms the Final Rule will inflict across the entire agricultural value chain. These harms include lost investment in tens

[6] *See* October 12, 1993 Memorandum for Heads of Executive Departments and Agencies and Independent Regulatory Agencies, App'x C, Regulatory Actions Exempted from Centralized Regulatory Review for the Office of Pesticides and Toxic Substances at EPA, at 15 ("Actions regarding pesticide tolerances, temporary tolerances, tolerance exemptions, and food additives regulations, except those that make an existing tolerance more stringent.").

of millions of dollars of chlorpyrifos products that can no longer be sold, distributed, or used, tens of millions of dollars annually in future lost sales, millions of dollars in needlessly discarded food and feed, and harms to the registrant, including damaged customer goodwill, reputational harm, and potential loss in market share. Seethapathi Decl. ¶¶ 41–49. Not to mention severe financial hardship to U.S. growers facing the possibility of significant crop losses as a result of the Final Rule. Indeed, by EPA's own estimates the economic value of chlorpyrifos to the U.S. economy is as high as $130 million annually, based only on the cost of alternative products; EPA's benefits assessment expresses no uncertainty as to these figures. *See* Revised Benefits at 5. This value is likely much higher in actuality for those growers without viable alternatives to control destructive insect pests who face yield losses if the Final Rule takes effect.

In sum, EPA had an obligation to seek OIRA review for a rule of this magnitude. EPA must immediately withdraw or stay the effective date of the Final Rule, pending the completion of appropriate interagency review processes.

K. OBJECTION 11: EPA's Application of a 10X FQPA Safety Factor to Account for "Uncertainties" in Unreliable Epidemiology Data is Arbitrary and Capricious.

EPA correctly confirmed in the Final Rule that there are no causal linkages between chlorpyrifos exposure and the neurodevelopmental effects alleged in certain epidemiology studies. 86 Fed. Reg. at 48,324. However, Gharda objects to EPA's application of a 10X FQPA safety factor to address "uncertainties" in epidemiology studies claiming neurodevelopmental impacts associated with chlorpyrifos exposure. As detailed in Gharda's comments on the PID, incorporated here by reference, the FFDCA does not support the application of a precautionary 10X safety factor to address "uncertainties" in scientific studies that do not meet basic standards of reliability, particularly where a 10X safety factor results in the elimination of many important crop uses.

The FFDCA, as amended by the FQPA, instructs EPA to make safety factor determinations based on "reliable data." This is made explicit in the statutory text—both the provision defining the "reasonable certainty [of] no harm" standard, FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii), and the provision addressing an additional 10-fold margin of safety. *Id*. § 408(b)(2)(C)(ii), § 346a(b)(2)(C)(ii). Thus, EPA actions to revoke tolerances and/or to increase a safety factor in such a way that effectively results in revocation must, by statute, be based on valid, reliable data.

The FFDCA does not define "reliability" or "reliable data." In guidance, EPA has counseled that "the data and information" relied upon to inform a safety factor determination "must be *sufficiently sound* such that OPP could routinely rely on such information in taking regulatory action." EPA, *Determination of the Appropriate FQPA Safety Factor(s) in Tolerance Assessment* (Feb. 28, 2002) ("FQPA Safety Factor Policy") at A-6 (emphasis added); *see also id.* at 29, 31 ("As part of the toxicological considerations, OPP evaluates potential pre- and postnatal toxicity on a case-by-case basis taking into account all pertinent information. . . . As in any weight-of-evidence approach, it is important to consider the *quality and adequacy of the data*, and the consistency of responses induced by the chemical across different studies.") (emphasis added). Data that are not replicable, and in some cases not available, are not reliable. EPA, *Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment for Pesticides*, at 30 (Dec. 28, 2016) ("[R]eliability general[ly] refers to the ability to reproduce results . . . ."). And, data that do not accurately reflect exposure are not valid. *Id.* ("[V]alidity generally refers to the extent that exposure estimates reflect true exposure levels.").

The epidemiology studies claiming neurodevelopmental effects from chlorpyrifos exposure suffer from significant limitations and deficiencies that render them unsuitable to guide

major regulatory action. The studies have been consistently criticized in public comments and by EPA's Scientific Advisory Panel as nontransparent, biologically implausible, lacking in validity, and unsupported by the weight of the evidence (including newer lines of epidemiology studies), among other issues. EPA itself has deemed the epidemiology data not sufficiently "valid, complete, and reliable . . . under the FFDCA," 84 Fed. Reg. at 35,557, and again acknowledged the limitations in the data in the Final Rule. 86 Fed. Reg. at 48,322. These studies simply do not meet basic standards of reliability sufficient to justify application of a 10X FQPA safety factor, particularly where this results in the elimination of many critical crop uses.[7] In sum, FQPA safety factors must be based on valid, reliable data, not "uncertainties."

VII. CONCLUSION

For these reasons, and because of the significant, immediate, and irreparable injuries Gharda has and will continue to suffer as a result of the revocation of all tolerances, the Final Rule should be summarily reversed or, at a minimum, stayed pending administrative review by EPA and any potential judicial review of the objections submitted by Gharda, growers, grower groups, and other adversely affected stakeholders.

[7] Indeed, the former EPA official who co-authored the FQPA Safety Factor Policy has observed in comments that "the FQPA safety factor has been primarily used to account for incompleteness or uncertainties in the animal toxicology data base," and applying a 10X FQPA safety factor based on questionable epidemiology data would be contrary to EPA policy. Decls. In Support of Dow AgroSciences LLC's Responses to Objections to EPA's Denial of Petition to Revoke All Tolerances and Cancel All Registrations for Chlorpyrifos, Decl. of Jennifer Seed ¶¶ 16, 21–23, EPA-HQ-OPP-2007-1005-0526 (Aug. 27, 2018).

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Chlorpyrifos Registrant

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE ADMINISTRATOR

In re:	)	
Tolerance Revocations: Chlorpyrifos.	)	FFDCA-HQ-2021-0001 (EPA-HQ-OPP-2021-0523)
	)	BUSINESS CONFIDENTIALITY ASSERTED

PETITION OF GHARDA CHEMICALS INTERNATIONAL, INC. TO STAY THE EFFECTIVE DATE OF THE REVOCATION OF ALL TOLERANCES FOR CHLORPYRIFOS

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Chlorpyrifos Registrant

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I. INTRODUCTION

On August 30, 2021, the U.S. Environmental Protection Agency ("EPA" or the "Agency") issued a final rule revoking all tolerances for the pesticide chlorpyrifos. Final Rule for Chlorpyrifos Tolerance Revocations, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"). This action was taken in response to an April 29, 2021 order of the U.S. Court of Appeals for the Ninth Circuit in the lawsuit *League of United Latin American Citizens v. Regan*, 996 F.3d 673, 678 (9th Cir. 2021) ("LULAC"), instructing EPA to "either to modify chlorpyrifos tolerances and concomitantly publish a finding that the modified tolerances are safe," "or to revoke all chlorpyrifos tolerances." Rather than modify tolerances consistent with the finding of its expert scientists that eleven key crop uses in select regions are currently safe, as set forth in the Agency's December 2020 Proposed Interim Decision for Chlorpyrifos, EPA-HQ-OPP-2008-0850-0971 ("PID"), EPA revoked *all* tolerances for chlorpyrifos. EPA did so because it claimed that it is required under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 346a to assess aggregate exposure risks taking into account all "currently registered uses" and that, when taking into account drinking water exposures, it could not conclude that "the products as currently registered" are safe. The Final Rule states that tolerances will expire six months from the date of publication, on February 28, 2022. 86 Fed. Reg. at 48,336.

Established in 1967, Gharda Chemicals International, Inc. ("Gharda") is a research-based agrochemical manufacturing company with offices in the United States. Declaration of Ram Seethapathi ("Seethapathi Decl.") ¶ 5. One of Gharda's main products is chlorpyrifos, for which Gharda holds a U.S. EPA registration. *Id.* Gharda sells end-use chlorpyrifos products under the brand name Pilot™ as well as technical grade chlorpyrifos for manufacturing use. *Id.* Immediately prior to the Final Rule, Gharda was the primary supplier of chlorpyrifos for agricultural uses in the United States. *Id.* ¶ 10. Accordingly, Gharda is an "adversely affected"

party, and is entitled to file objections on the issues relevant to this action. 40 C.F.R. § 178.20. Gharda's objections to the Final Rule are incorporated by reference here.

Gharda is challenging the legal and factual sufficiency of the Final Rule by exercising its right to file objections. Specifically, EPA has abused its discretion, acted arbitrarily and capriciously, and violated the due process rights of Gharda and others by revoking all chlorpyrifos tolerances despite conceding in its own risk assessment that eleven key crop uses in select states are currently safe, and in disregard of a written commitment from Gharda to modify its registration in accordance with the Agency's safety finding. EPA's Final Rule is at odds with its statutory directive under the FFDCA to assess risks from "anticipated" exposures, not exposures based on uses the Agency *previously* approved, and would lead to the absurd result that EPA could never modify tolerances to limit use of a previously registered product based on new or updated scientific data.

Among other issues, the Final Rule is fatally flawed because it ignores relevant scientific data, including (i) comments on and proposed refinements to the 2016 drinking water assessment EPA relied on to revoke tolerances, (ii) the Agency's updated, more highly refined, and peer-reviewed 2020 drinking water assessment, and (iii) a drinking water study of chlorpyrifos oxon (the chlorpyrifos metabolite that exists in drinking water following chlorination) submitted by the registrants that significantly undermines EPA's assumptions concerning drinking water risk concerns. EPA's failure to adequately consider and respond to highly relevant scientific data and comments that bear directly on the drinking water concerns EPA used to justify a revocation of all tolerances is arbitrary and capricious and raises significant due process concerns. EPA's Final Rule also improperly revokes import tolerances the Agency conceded in the PID are safe, and incorrectly applies a precautionary Food Quality Protection Act ("FQPA") safety factor of

10X to address "uncertainties" in epidemiology studies the Agency has acknowledged do not meet basic standards of reliability.

Apart from lacking any reasoned or logical scientific justification, the portions of the Final Rule objected to herein impose an unreasonable and effectively meaningless six-month implementation period. The Final Rule will have catastrophic consequences for all members of the agricultural value chain. EPA has also failed to harmonize the Final Rule with the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), including by abdicating its responsibility to oversee the safe, lawful, and orderly phase-out of existing stocks of chlorpyrifos products that will soon be rendered unusable as a result of the Final Rule. The Agency also disregarded cancellation procedures and interagency review processes intended to notify the public and other affected parties of actions like the one taken here that will significantly impact the agricultural economy.

Finally, EPA's decision followed months of discussions with Gharda concerning a voluntary cancellation of uses, during which Gharda committed to meeting each of EPA's continually increasing and unjustified demands, in a good-faith effort to cooperate with the Agency. EPA led Gharda to believe that the parties were close to finalizing a voluntary cancellation agreement with EPA that would allow key crop uses to continue—key crop uses that *EPA had found safe* in the PID—when the Agency suddenly withdrew from these discussions, without a scientific basis or explanation to Gharda, and revoked all tolerances. EPA's conduct and processes leading up to the Final Rule ignored its own science and were fundamentally unfair and demonstrate bad faith, further undermining the reasonableness of the Agency's decision-making.

For these reasons and as outlined more fully below, and because of the significant, immediate, and irreparable injuries Gharda and others have and will continue to suffer as a result of the revocation of all tolerances, the Final Rule and expiration of chlorpyrifos tolerances should be summarily reversed or, at a minimum, stayed pending administrative review by EPA and any potential judicial review of the objections submitted by Gharda, growers, grower groups, and other adversely affected stakeholders. Consistent with its repeated commitments to EPA prior to the Final Rule, Gharda respectfully requests that, at a minimum, EPA retain the tolerances for the 11 key crops found safe in the PID.

II. REQUEST FOR STAY

Gharda hereby requests that the Final Rule be summarily reversed or, at a minimum, requests a stay of the effective date of the Final Rule and the expiration date for chlorpyrifos tolerances. Gharda requests that the stay of the effective date of the Final Rule and expiration of tolerances remain in effect until a final Agency resolution of all of the critical issues raised by the objections of Gharda, growers, grower groups, and other adversely affected stakeholders. If these issues are not resolved in Gharda's favor by the Agency's final order addressing these issues, Gharda further requests that the Agency stay the effective date of any revocation action and tolerance expiration until such time as judicial review in the courts is exhausted.

III. GHARDA HAS MET THE CRITERIA FOR A STAY

For the reasons presented herein, and discussed in detail in Gharda's objections and supporting documentation, which are incorporated into this petition by reference, Gharda submits that it has met the criteria for a stay of administrative decision set forth by the Food and Drug Administration ("FDA") at 21 C.F.R. § 10.35.[1] Under this criteria, a stay will be granted

[1] EPA has stated that it relies on the criteria set forth in FDA's regulations regarding stays of administrative proceedings at 21 C.F.R. § 10.35. 74 Fed. Reg. at 23,088.

if: (1) the petitioner will otherwise suffer irreparable injury; (2) the petitioner's case is not frivolous and is being pursued in good faith; (3) the petitioner has demonstrated sound public policy grounds supporting the stay; and (4) the delay resulting from the stay is not outweighed by public health or other public interests. *Id.* § 10.35(e)(1)–(4) (as amended by 81 Fed. Reg. 78,500 (Nov. 8, 2016)).

A. Gharda Will Suffer Irreparable Injury.

In order to demonstrate irreparable harm, a party must show both "(1) that the harm is 'certain and great, actual and not theoretical, and so imminent that there is a clear and present need for equitable relief to prevent irreparable harm' and (2) that the harm is 'beyond remediation.'" *Catholic Legal Immigration Network, Inc. v. Executive Office for Immigration Review*, 513 F. Supp. 3d 154, 175 (D.D.C. 2021) (citation omitted); *see also Olu-Cole v. E.L. Haynes Pub. Charter Sch.*, 930 F.3d 519, 529 (D.C. Cir. 2019) (to show irreparable harm, "injury must be both certain and great; it must be actual and not theoretical and of such imminence that there is clear and present need for equitable relief") (internal quotation marks and citations omitted). Irreparable injury can be based on substantial and unrecoverable economic losses, such as lost sales and loss of market share, as well as other losses like damaged consumer goodwill or reputational harm. Indeed, courts have found the irreparable harm requirement met where many forms of irreparable injury are alleged, including "reputational harm, loss of goodwill, loss of longstanding clients, loss of ability to compete for and attract new clients and partners, incalculable lost profits, and consequential damages for which [petitioner] has no recourse at law." *Beacon Assocs., Inc. v. Apprio, Inc.*, 308 F. Supp. 3d 277, 287–88 (D.D.C. 2018).

Losses for which an aggrieved party has no recourse, such as those caused by a governmental entity immune from suit for monetary relief, are "irreparable *per se*." *Feinerman*

v. Bernardi, 558 F. Supp. 2d 36, 51 (D.D.C. 2008); *see also Nalco Co. v. EPA*, 786 F. Supp. 2d 177, 188 (D.D.C. 2011) (seller of anti-microbial agent would suffer irreparable harm from EPA stop sale order because it had no right of recourse against the federal government). Additionally, a due process violation, such as the deprivation of a legally protectable property right (*i.e.*, pesticide registration), constitutes irreparable harm. *See Blackman v. District of Columbia*, 277 F. Supp. 2d 71, 79 (D.D.C. 2003) (due process violations fulfill the irreparable injury requirement for a preliminary injunction); *see also Padberg v. McGrath-McKenchnie*, 108 F. Supp. 2d 177 (E.D.N.Y. 2000) (deprivation of a government-issued license constituted irreparable harm); *Small Hearts Daycare, II, LLC v. Quick*, No. 09CV2132, 2010 WL 427766, at *1 (E.D. Mo. Feb. 1, 2010) (same); *see also Reckitt Benckiser, Inc. v. Jackson*, 762 F. Supp. 2d 34, 45 (D.D.C. 2011) ("A FIFRA registration is essentially a license to sell and distribute pesticide products in accordance with the terms of the registration and the statute.").

The Final Rule has caused and will continue to cause significant and irreparable harm to Gharda that is both imminent and beyond remediation, requiring a clear and present need for equitable relief in the form of an administrative stay. The Final Rule revokes all tolerances for chlorpyrifos effective on February 28, 2022, after which tolerances will be "expired" and chlorpyrifos can no longer be distributed, sold, or used. This six-month time period is effectively meaningless and allows no time for Gharda, distributors, and growers to phase out and exhaust existing inventories. Seethapathi Decl. ¶ 41. This will result in devastating financial losses to Gharda, which earlier this year had increased production to meet market demand for chlorpyrifos after Corteva's exit from the market and, as a result, now has a significant volume of raw materials and U.S.-labeled product in inventory. *Id.*. ¶ 42. Without the ability to formulate, distribute, and sell these products, Gharda will suffer Redacted - CBI economic losses, to say

nothing of the nearly Redacted - CBI loss in its investment in chlorpyrifos and lost future sales of chlorpyrifos products in the U.S. of approximately Redacted - CBI annually. *Id.* In total, the economic losses Gharda will face if the Final Rule is not reversed or rescinded will be catastrophic. *Id.*

Beyond these economic losses, Gharda has suffered and will continue to suffer significant reputational harm as a result of EPA's arbitrary action against chlorpyrifos. *Id.* ¶ 43. By revoking all tolerances, EPA has directly attacked the safety of chlorpyrifos in the eyes of growers, processors, and consumers, and the credibility of Gharda in selling and distributing chlorpyrifos products. *Id.* EPA has done this despite a finding by its own expert scientists that a subset of eleven high-benefit chlorpyrifos uses in certain geographic areas are safe, and in disregard of written commitments by Gharda ***prior to the Final Rule*** to modify Gharda's label consistent with EPA's safety finding in its PID. *Id.*; *see also Jones v. District of Columbia*, 177 F. Supp. 3d 542, 547 (D.D.C. 2016) (citations omitted) (reputational injury can be used to establish irreparable); *Xiaomi Corp. v. Dep't of Def.*, Civ. A. No. 21-280, 2021 WL 950144, at *1, *10 (D.D.C. Mar. 12, 2021) (reputational damage, in conjunction with serious unrecoverable financial harm, weighs in favor of granting preliminary relief).

EPA's revocation action has and will continue to strain Gharda's relationships with its customers, who distribute its products to suppliers and end users. Seethapathi Decl. ¶ 44. Indeed, during its months of negotiations with EPA, Gharda assured its customers that it was working cooperatively with EPA to reach agreement that would allow for many continued agricultural uses. *Id.* Given EPA's scientific assessment in the PID which provided a clear scientific record on which to retain *at least* the 10X uses, neither Gharda nor its customers expected that EPA would take draconian action to eliminate *all* uses. *Id.* EPA's abrupt

departure from its own scientific findings has cast doubt on Gharda's credibility and resulted in a loss of customer goodwill. *Id.*

In addition to the immediate and irreparable harm caused by Gharda by EPA's action, EPA's revocation action could create long-term irreparable harm to Gharda because of the stigma attached to the unfounded public statements by EPA that its action was taken "to ensure children, farmworkers, and all people are protected from the potentially dangerous consequences of this pesticide," and "follow[s] the science and put[s] health and safety first."[2] *Id.* ¶ 45. There is no scientific basis for these statements, which are in fact directly at odds with EPA's Final Rule and the scientific findings set forth in the PID. *Id.* (citing 86 Fed. Reg. at 48,324 (EPA "remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported by [epidemiology studies reporting neurodevelopmental impacts in children]" *id*. at 48,335 ("EPA has not conducted a formal EJ analysis for this rule"); PID at 10 ("the science addressing neurodevelopmental effects remains unresolved").

The stigma attached to EPA's public statements not only has the potential to cause ill-will against Gharda by customers, consumers, and the public, but will also adversely affect Gharda's ability to meet the needs of growers for effective pesticide products, compounding the ill-will against Gharda. Seethapathi Decl. ¶ 46. Customers who abandon Gharda products now because of the Agency's action may not return to using products produced by Gharda even in the event of a final adjudication in Gharda's favor. *Id.* Gharda may thus permanently lose a significant portion of its market share. *Id.* Moreover, EPA's actions may trigger other federal or state regulatory requirements or bans, as well as restrictions by foreign governments, who look to

[2] EPA, *EPA Takes Action to Address Risk from Chlorpyrifos and Protect Children's Health,* https://www.epa.gov/newsreleases/epa-takes-action-address-risk-chlorpyrifos-and-protect-childrens-health (Aug. 18, 2021).

EPA as the gold standard for making regulatory decisions based on science. *Id.*

Losses from an immediate removal of chlorpyrifos from the U.S. market would not be borne by Gharda alone. *Id.* ¶ 47. It will also cause significant financial hardship to distributors and growers who invested substantial sums in reliance on the registration in products they are no longer able to sell or use. *Id.* Most distributors purchase products from Gharda at least a year in advance, and as a result have significant product on hand in order to meet market needs and often fluctuating demand by U.S. growers. *Id.* Gharda has been specifically informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI. *Id.* Growers, for their part, not only face a lost investment in unusable products but also must find alternative, sometimes more expensive alternative products or risk significant crop losses. *Id.* In total the volume of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers is estimated to be valued at Redacted - CBI. *Id.* Moreover, by insisting on giving immediate effect to the revocation actions, EPA has caused confusion on the part of the public with respect to the safety of dozens of commodities on which chlorpyrifos may legally be used. *Id.* ¶ 49.

In short, Gharda has readily satisfied the irreparable harm requirement for an administrative stay, given the significant and irreparable harm it has and will continue to suffer as a result of EPA's Final Rule.

B. Gharda's Case Is Not Frivolous And Is Being Pursued In Good Faith.

Gharda's case is not frivolous and is being pursued in good faith. Gharda has submitted nearly fifty pages of objections to the Final Order setting forth in detail the numerous substantive and procedural flaws in the Final Order, and the grounds for its objections, with supporting authorities, documentation, and declarations. The objections and supporting materials Gharda has submitted demonstrate, among other things, that the alleged basis for EPA's revocation of all

tolerances of chlorpyrifos lacks any scientific support, is contrary to EPA's own safety finding and its consistent regulatory practice, and is at odds with text of the FFDCA and the Ninth Circuit order. Gharda's objections also demonstrate that EPA has also abridged the due process rights of Gharda and other affected parties in issuing the Final Rule, including by refusing to engage in meaningful review of highly relevant scientific data and other information that *directly address* the alleged drinking water concerns EPA relied on to revoke all tolerances. Gharda has more than demonstrated that it is pursuing its case with great seriousness and in good faith to rectify the Agency's arbitrary and unlawful action.

C. Gharda Has Demonstrated Sound Public Policy Grounds Supporting The Stay Request.

Gharda's objections demonstrate that sound public policy grounds support its stay request. Substantively, EPA's Final Rule ignores the fulsome and carefully considered assessments of Agency expert scientists demonstrating that there are safe uses for chlorpyrifos that can and should remain approved, without any logical or reasoned explanation. Good public policy does not support regulatory decisions that blatantly override the Agency's best available science, particularly a decision of this magnitude.

Procedurally, the Agency has issued the Final Rule in a manner that is fundamentally unfair and demonstrates bad faith, by abruptly revoking tolerances after months of discussions with Gharda concerning a voluntary cancellation that would have allowed many key agricultural uses to continue, consistent with the Agency's safety finding. The Agency also disregarded cancellation procedures and interagency review processes intended to notify the public and other affected parties of actions like the one taken here that will significantly impact the agricultural economy, and abdicated its responsibility to oversee a lawful and orderly phase-out of products, including existing stocks. Sound public policy dictates that a government agency issue rules and

regulations affecting the rights and interests of regulated parties and the public in a reasonable, even-handed, and transparent manner.

Practically, the Agency's Final Rule ignores the realities of the agricultural economy by imposing an impossibly short timeframe for tolerance expiration that allows no meaningful time for Gharda, its distributors, and growers to exhaust existing inventories of chlorpyrifos and that will result the needless waste of safe and wholesome food. Seethapathi Decl. ¶ 41. The Final Rule will also cause significant hardship to U.S. growers who will be forced to rely on more expensive and/or less effective products to meet their crop protection needs. *Id.* 48. Increased pesticide applications could also impact the environment. In short, Gharda has amply demonstrated that there are strong public policy grounds favoring a stay.

D. The Delay Resulting From The Stay Is Not Outweighed By Public Health Or Other Public Interests

There are no public health or other public interests that will be adversely impacted by granting a stay. The safety of chlorpyrifos is supported by decades of scientific study. Few pest control products have undergone this level of scientific review. EPA itself has conceded that eleven key crop uses in select geographic are safe. Its assessments as to the remaining uses ignore relevant data and information that address the alleged drinking water risk concerns and are otherwise predicated on incorrect application of a precautionary 10X FQPA safety factor, which cannot be used to address "uncertainties" in unreliable data concerning alleged neurodevelopmental effects. In contrast, if not stayed, the Final Rule will wreak havoc on the agricultural economy, significantly and irreparably harm Gharda and other affected parties, and negatively impact the environment.

IV. CONCLUSION

For all the above reasons, granting a stay is in the public interest and in the interest of

justice. Therefore, Gharda requests that the Agency grant this petition for a stay of the effective date of the Final Rule and the expiration date for chlorpyrifos tolerances until a final resolution, including potential judicial review, is reached on all of the critical issues raised in Gharda's objections.

Respectfully submitted,

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Chlorpyrifos Registrant

October 22, 2021

Declaration of Ram Seethapathi

I, Ram Seethapathi, declare as follows:

1. I am the President of Gharda Chemicals International, Inc. ("Gharda"). I am authorized to make this affidavit on behalf of Gharda and have personal knowledge of all facts set forth herein.

2. I have a degree in Agricultural Sciences with a specialization in Entomology from Tamil Nadu Agricultural University; I was a Gold Medalist there, with a 4.0 GPA. I also have a diploma in General Management from the Indian Institute of Management Ahmedabad. I have been working for over four decades in the agricultural chemical industry at various levels, first in field development with Bayer, then as Regional Sales manager for Shell, and finally for eighteen years with Dow AgroSciences LLC (now Corteva Agriscience) in the Agricultural Chemicals Division, with progressively increasing responsibilities as Commercial Manager, Business Leader, and Human Resources Leader. While at Dow AgroSciences, I was involved very closely in chlorpyrifos market expansion from the early phase of the product lifecycle, including assisting in establishing a new manufacturing site in India and providing extensive training to employees working there. I was also the Safety Coordinator for Dow AgroSciences for the Asia Pacific region. I joined Gharda fourteen years ago, providing leadership for their business in North America.

3. I also serve as Administrative Committee Chair for two important Industry taskforces, the Outdoor Residential Exposure Taskforce (ORETF) and the Agricultural Re-entry Taskforce (ARTF). In addition, I serve on the Executive Committee for the Agriculture Handler Exposure Taskforce (AHETF). These taskforces are consortia of agrochemical companies that coordinate to jointly develop scientific studies in support of pesticide registrations.

4. I submit this affidavit in support of Gharda's Petition to Stay the Effective Date of the U.S. Environmental Protection Agency's ("EPA's" or the "Agency's") Final Rule for Chlorpyrifos Tolerance Revocations, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule") and Gharda's Objections to the Final Rule.

Background on Gharda and Its Role in the Chlorpyrifos Market

5. Established in 1967, Gharda is a research-based company leading in the field of agrochemical manufacturing. Gharda was founded by Dr. Keki Hormusji Gharda, a prominent chemical engineer and chemist. After obtaining a Masters degree and Ph.D. in Chemical Engineering from the University of Michigan, Ann Arbor, Dr. Gharda established Gharda Chemicals in a small rented shed. More than four decades of innovation and investment in R&D has transformed Gharda into a successful pioneer agrochemical company. Gharda's product portfolio includes a wide range of insecticides and herbicides, including chlorpyrifos, for which it holds an EPA registration. Gharda sells end-use chlorpyrifos products under the brand name Pilot™ as well as technical grade chlorpyrifos for manufacturing use.

6. Chlorpyrifos is a vitally important agricultural tool, protecting over fifty valuable U.S. food crops from destruction due to insect pests, including alfalfa, cotton, soybeans, sugarbeets, and wheat. Crops protected by chlorpyrifos are worth over a hundred million dollars annually to the U.S. economy. *See* EPA, Revised Benefits of Agricultural Uses of Chlorpyrifos at 5, 7, EPA-HQ-OPP-2008-0850-0969 (Nov. 18, 2020) ("Revised Benefits"). Chlorpyrifos has value to growers in protecting their crops and income, as well as value to consumers who enjoy affordable, healthy, and high quality produce throughout the year.

7. Chlorpyrifos's critical importance as an insect pest management tool is due to its broad-spectrum efficacy, favorable environmental characteristics, and affordability for growers.

It is the leading active ingredient to control a broad spectrum of difficult-to-control insect pests, and for some destructive pests it is the only effective pest management tool available. *Id.* at 2.

8. Because of its broad-spectrum effectiveness, chlorpyrifos is often the first tool growers employ to control new or unknown insect pests, a long-standing problem but one that will be exacerbated by climate change. *See id.* at 12–13 (removal of "broad spectrum materials such as chlorpyrifos . . . from pest management programs can result in unexpected outbreaks of previously minor pests or even the emergence of new pests"). Chlorpyrifos is also less harmful to beneficial insect populations than other insecticides. It requires fewer applications and avoids the use of multiple chemistries to control certain pests, reducing overall insecticide use.

9. Gharda has long supported the registration of chlorpyrifos in the United States, including through an industry task force that provided financial and other support for comments, scientific data, and other materials submitted to EPA by Dow AgroSciences, LLC, now Corteva Agriscience.[1] Gharda has invested over Redacted - CBI in the development of data and other information to support the registration of chlorpyrifos in the United States.

10. In February 2020, Corteva announced that it would end production of chlorpyrifos by 2021. At that time, chlorpyrifos continued to be a critically important agricultural tool for many growers. As a result, many distributors and farm input suppliers began looking to Gharda to meet the market demand for chlorpyrifos. In response to this increase in demand, Gharda significantly increased its production of chlorpyrifos. Immediately prior to the Final Rule, Gharda was the primary supplier of chlorpyrifos for agricultural use in the United States.

[1] A list of many of the prior comments and submissions Gharda has supported through the task force is attached as Appendix A and incorporated herein by reference and in Gharda's Objections to the Final Rule.

11. Chlorpyrifos is one of Gharda's most important products. Revenues from sales of chlorpyrifos comprise a significant portion of Gharda's overall U.S. business, which prior to the Final Rule was only expected to increase. In 2020, Gharda's annual U.S. revenues from chlorpyrifos were approximately Redacted - CBI. 2021 U.S. revenues from chlorpyrifos total Redacted to date and prior to the Final Rule were expected to increase to Redacted - CBI by year end. In 2022 and beyond, Gharda's annual U.S. revenues from chlorpyrifos were projected (before the Final Rule) to be approximately Redacted - CBI annually.

12. Gharda's position in the U.S. agrochemical industry is unique. Unlike many other registrants and leading suppliers of crop protection tools in the United States, Gharda does not have U.S.-based manufacturing facilities, which adds an additional level of complexity to the supply chain not encountered by U.S.-based manufacturers. Gharda ships materials to the United States and then uses tolling companies to package and label the technical and end use chlorpyrifos products for sale to U.S. distributors, creating significant employment opportunities. The pandemic has exponentially increased the costs and time required to ship Gharda's materials to the U.S. for formulating, packaging, and labeling.

13. Currently, Gharda has a significant volume of raw materials on hand at its manufacturing facility in India. Gharda also has inventory of U.S. labeled chlorpyrifos product on hand at its India facility valued at Redacted - CBI. In addition, Gharda has inventories of chlorpyrifos product ready for distribution in the U.S. valued at Redacted - CBI. If Gharda is unable to formulate, sell, and distribute these products for use in the 2022 growing season and beyond, Gharda will suffer Redacted - CBI economic losses. These losses are in addition to the Redacted - CBI lost investment described above in Paragraph 9 and future annual lost sales similar to those set forth above in Paragraph 11.

14. There are also significant stores of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers, estimated to be valued at approximately Redacted - CBI. (Gharda has been specifically informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI.)

EPA's Regulatory Processes Concerning Chlorpyrifos

15. Gharda has a vital interest in pesticide regulatory procedures and food safety standards, and in actions taken by the EPA with respect to agricultural crop protection tools, including actions that relate to pesticide residues found in or on food and the regulation of those residues under the Federal Food, Drug, and Cosmetic Act ("FFDCA") and Food Quality Protection Act ("FQPA"), and associated pesticide registration actions under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA").

16. On December 7, 2020, as part of its Registration Review of chlorpyrifos pursuant to FIFRA, EPA published its Proposed Interim Registration Review Decision for Chlorpyrifos, EPA-HQ-OPP-2008-0850-0971 (the "PID"). *See* 85 Fed. Reg. 78,849 (Dec. 7, 2020). The PID is supported by analyses included in EPA's September 21, 2020 Third Revised Human Health Risk Assessment, EPA-HQ-OPP-2008-0850-0951 (the "2020 RHHRA"), which in turn relies on, among other documents, a September 15, 2020 Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review, EPA-HQ-OPP-0850-0941 (the "2020 DWA"). EPA's PID and 2020 DWA reflected a fulsome, measured, scientific assessment of the human health and drinking water risks of chlorpyrifos by EPA's expert scientists.

17. In its 2020 RHHRA and PID, EPA continued to use 10% red blood cell acetyl cholinesterase inhibition ("RBC AChE") as a regulatory endpoint or point of departure for human health risk assessments for chlorpyrifos. *See* 2020 RHHRA at 2. This long-standing

conservative and health-protective endpoint is supported by decades of scientific study. EPA stated that it "remains unable to verify the reported findings" of epidemiology studies claiming links between prenatal exposure to chlorpyrifos and neurodevelopmental effects. 2020 RHHRA at 89–90.

18. EPA's PID relied on the 2020 DWA, which updated and refined the Agency's 2016 DWA. In the 2020 DWA, EPA focused on eleven uses (alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugar beet, strawberry, and wheat) that EPA determined to be high-benefit, critical crop uses. PID at 15–17. The 2020 DWA focused on select regions of the country where estimated drinking water concentrations of chlorpyrifos are below the drinking water level of concern. *Id*. In the 2020 RHHRA and PID, EPA conducted an assessment of potential risk to human health from aggregate exposure to chlorpyrifos residues, taking into account all anticipated dietary exposures from food, drinking water, and residential sources, pursuant to FFDCA Section 408(b). EPA determined that there were *no* potential risks of concern from exposure to chlorpyrifos in food or residential uses alone. 2020 RHHRA at 12; PID at 14, 18. EPA determined that risks from drinking water exposure exceeded safe levels taking into account *all* registered uses but, relying on its 2020 DWA, EPA found that risks were *below* the drinking water level of concern benchmark anticipating use only on the eleven high-benefit crops set forth above in certain identified regions of the country. PID at 18.

19. In its 2020 RHHRA and PID, EPA presented two potential approaches for assessing potential risks: (i) application of a 10X FQPA safety factor and limiting use of chlorpyrifos to the eleven high-benefit agricultural uses in select regions of the country due to "uncertainty" in "the science addressing neurodevelopmental effects," or (ii) application of a 1X FQPA safety factor, which would allow for the retention of all currently registered uses.

Regarding the first approach, EPA was unequivocal that "the agency has determined" that limiting use to the eleven "high-benefit agricultural uses" in the select geographic regions "**will not pose potential risks of concerns with an FQPA safety factor of 10X**." PID at 40 (emphasis added). EPA committed to "consider registrant and stakeholder input on the subset of crops and regions from the public comment period" and stated that it "may conduct further analysis to determine if any other limited uses may be retained." *Id.* EPA also indicated that it may further refine its assessment based on feedback and recommendations from the September 2020 FIFRA Scientific Advisory Panel. *Id.*

20. Gharda submitted comments on the PID on February 3, 2021. EPA-HQ-OPP-2008-0850-0999. Gharda urged that the weight of the scientific evidence supported application of a 1X FQPA safety factor, including a recent Corteva drinking water study of chlorpyrifos oxon submitted to the EPA on December 4, 2020, which shows that there are no drinking water risk concerns associated with chlorpyrifos oxon (the chlorpyrifos metabolite that exists in drinking water following chlorination). *See A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days*, MRID 51392601.

Gharda's Discussions With EPA Concerning a Potential Voluntary Cancellation of Chlorpyrifos Uses

21. In April 2021, EPA regulatory personnel reached out to me to discuss whether Gharda would entertain an agreement to voluntarily cancel some uses of chlorpyrifos. These discussions focused initially on uses identified in the PID as the 1X uses. EPA proposed a meeting with Gharda on April 20, 2021, and requested that Gharda confirm in writing in advance of that meeting Gharda's commitment to voluntarily cancel the 1X uses (while retaining the eleven high benefit crop uses identified as the 10X uses). In response, even though Gharda was

confident that all 1X uses are well supported, Gharda indicated that it would consider phasing out some 1X uses on a reasonable timetable and adopting potential geographic restrictions on crop uses and other risk mitigation measures. *See* Exhibit A. Gharda expressed concern with the Agency's proposed rushed timetable, however, given the impact of a phase-out on its business and on the grower community, and given that EPA had not yet reviewed stakeholder comments on the PID. *Id.* EPA cancelled the meeting with Gharda in order to discuss Gharda's letter further internally.

22. On April 29, 2021, the Ninth Circuit issued a decision in the lawsuit *League of United Latin American Citizens v. Regan*, consolidated Case Nos. 19-71979, 19-71982 ("*LULAC*"), which concerned EPA's handling of an administrative petition to revoke all tolerances filed by several nongovernmental organizations. In a 2-1 decision, a three-judge panel of the Ninth Circuit found that EPA's denial of objections to a 2017 order denying the administrative petition was at odds with the FFDCA because EPA did not make an affirmative finding that chlorpyrifos tolerances were "safe" in response to the petition, outside of its normal regulatory processes. *LULAC*, 996 F.3d 673 (9th Cir. 2021). The Ninth Circuit ordered EPA "either to modify chlorpyrifos tolerances and concomitantly publish a finding that the modified tolerances are safe," "or to revoke all chlorpyrifos tolerances." *Id.* at 678 (emphasis added). In making this ruling the court expressly recognized the importance of the PID. Indeed, the court stated that:

> [D]uring the pendency of this proceeding, in December 2020, the EPA issued a Proposed Interim Registration Review Decision proposing to modify certain chlorpyrifos tolerances. The EPA also convened another SAP in 2020. **If, based upon the EPA's further research the EPA can now conclude to a reasonable certainty that modified tolerances or registrations would be safe, then it may modify chlorpyrifos registrations rather than cancelling them.**

Id. at 703. (emphasis added). The court ordered EPA to "correspondingly modify or cancel related FIFRA registrations for food use in a timely fashion consistent with the requirements of 21 U.S.C. § 346a(a)(1)." *Id.* at 678.

23. After the Ninth Circuit issued its decision in *LULAC*, EPA reached back out to me to resume discussions about a potential voluntary cancellation of certain chlorpyrifos uses. EPA career supervisory personnel strongly urged Gharda to agree to voluntarily cancel the 1X uses and emphasized that the Agency had limited time to decide how to implement the court's decision. In response, Gharda expressed its disagreement with the Ninth Circuit decision and hope that EPA would seek rehearing of and/or appeal the flawed decision. *See* Exhibit B. Nevertheless, in an effort to work cooperatively with EPA and believing it had little choice but to accept voluntary cancellation terms, Gharda committed to voluntarily cancel yet additional 1X crop uses, pursuant to scheduled phase-outs and with appropriate existing stocks orders. *Id.* EPA strongly implied during these discussions the 10X uses would remain in place as long as Gharda voluntarily cancelled all 1X uses. *Id.*

24. In further discussions with EPA career supervisory personnel in late May 2021, EPA expressed to Gharda that EPA was willing to consider retention of only the 10X uses, and reiterated that it was under pressure to act quickly as a result of the Ninth Circuit decision. EPA urged Gharda to confirm in writing its agreement to voluntarily cancel all 1X uses. In response, and even though such a reduction in uses would eliminate more than 50% of Gharda's U.S. chlorpyrifos business, Gharda committed to continue working in good faith with EPA towards an agreement to voluntarily cancel all 1X uses. *See* Exhibit C. To that end, **on June 7, 2021, Gharda confirmed in writing to EPA that it would voluntarily cancel all currently approved agricultural uses of chlorpyrifos, other than the uses identified in the PID as 10X**

uses. *Id.* In turn, Gharda requested that EPA (i) work with it to address the orderly exhaustion of its inventories for the uses to be voluntarily cancelled, particularly given its unique role in the U.S. agrochemical industry; (ii) agree on orderly processes and timing for revising labels; and (iii) agree on existing stocks provisions for the uses to be voluntarily cancelled, to mitigate disruption on growers and other users. *Id.*

25. EPA career supervisory personnel were receptive to Gharda's June 7 commitment, responding the next day to ask "if Gharda is prepared to move forward with discussing voluntary use cancellations" and proposing a call with EPA legal counsel. By email dated June 8, 2021, EPA indicated that it was "considering the following dates for existing stocks:

- Technical grade active ingredient: Phase out most [1X] uses by the end of 2021; allow until the end of 2022 (12 to 18 months) for the remaining [1X] uses
- End-use products: 12 to 18 months from the technical registrants for sale/distribution of products
- End users, growers: Until exhausted"

Exhibit D.

26. Gharda responded to EPA's June 8 email proposing a meeting with its attorneys, with the expectation that the parties were close to reaching final agreement on terms and could begin work on modifying labels. Exhibit E.

27. Then, on June 14, 2021, EPA career supervisory personnel advised Gharda that Gharda's commitment regarding the "voluntary" cancellation of uses were not sufficient for EPA's "leadership," and asked Gharda to consider voluntarily cancelling yet additional uses, this time including some 10X uses, or face possible revocation of all tolerances. EPA urged Gharda to agree to voluntarily cancel all but five to six of its most important crop uses. This was the first

time that EPA asked Gharda to consider voluntarily cancelling 10X crop uses. EPA also said that its leadership had raised occupational exposure concerns, and asked that Gharda agree to eliminate the use of aerial application methods, even though these are not issues to be addressed under FFDCA but are instead issues to be addressed in Registration Review under FIFRA's risk/benefit standard. In subsequent calls, EPA also expressed concerns regarding ecological risks from chlorpyrifos, even though the ecological risk assessment for chlorpyrifos has yet to be completed. EPA nevertheless continued to indicate openness to an extended phase-out period for any voluntarily cancelled uses.

28. Gharda was confused, surprised, and disappointed at EPA's request that Gharda agree to voluntarily cancel 10X uses that EPA had confirmed, in a robust scientific assessment in its PID, would not exceed safe levels. Gharda was also concerned that EPA appeared to be relying on occupational and ecological concerns as the basis for its request, neither of which relate to the regulation of tolerances under the FFDCA. Despite this dramatic and unexpected shift in the discussions, Gharda remained willing to work with EPA to try to meet its demands. Gharda repeatedly urged EPA to ensure an orderly phase-out for manufacturers, distributors, growers, and others in the agricultural supply chain for the uses to be voluntarily cancelled, as EPA's demand would eliminate nearly 80–85% of the U.S. market for chlorpyrifos.

29. Gharda and EPA had a meeting on June 24, 2021 to further discuss terms of Gharda's voluntary cancellation of registered crop uses. In a follow-up email dated June 24, 2021, approximately two months from the deadline for EPA to act in response to the Ninth Circuit order, ***EPA's Chemical Review Manager wrote Gharda*** "to confirm the uses that Gharda has agreed upon for retention following our discussions over the past few weeks and on our call this afternoon" and outlined the following terms:

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Cotton and strawberry will be phased out over two years (until 2023)
- Aerial application will be phased out over 2 years (until 2023)
- Provisions for existing stocks:
    - Technical products [with current labels] may be sold or distributed until 12/31/2021
    - End-use products [with current labels] may be sold or distributed until 12/31/2022

See Exhibit F.

30. In emails dated June 25, 2021, Gharda sought clarification from EPA on some aspects of its June 25 proposal, including the details of various phase-out periods. In these emails, Gharda thanked EPA "for our good faith negotiations over the last few weeks" and said that it "looks forward to working with the Agency to finalize the above terms." *See* Exhibit G. EPA proposed a meeting with its Office of General Counsel. It was Gharda's expectation that in involving legal counsel, the parties would be working to finalize a written agreement reflecting the agreed terms.

31. At EPA's request, on July 2, 2021, Gharda had a further call with EPA career supervisory personnel, during which EPA pressed Gharda to agree to voluntarily cancel even more 10X crop uses because of demands from EPA's leadership. EPA also indicated that it would not be able to agree to an extended phase out period and that chlorpyrifos applications would need to cease after six months, instead of the phase-out periods that ***EPA had proposed*** one week earlier in its June 24 email. *See* ¶ 29 & Ex. F. EPA also raised concerns with air blast applications on orchard crops. Gharda offered to provide data on mitigation measures that would address EPA's concerns regarding occupational exposure, but EPA said it would not consider mitigation data. EPA asked Gharda to put forward its best, final proposal that EPA would take back to its leadership. Gharda was especially surprised and disappointed with this turn of events,

as it in good faith believed that EPA's June 24 email, *see* ¶ 29 & Ex. F, had set forth the final terms of crop use retention and voluntary cancellation.

32. At EPA's request, Gharda had a call with EPA and its counsel on July 6, 2021. During the call EPA pressed Gharda to accept voluntary cancellation of all but three 10X uses and reiterated that it would be unable to allow use beyond six months from the effective date of a final rule. EPA explained that the six-month period was based on the WTO Agreement on the Application of Sanitary and Phytosanitary measures, not because of a need for the orderly phase-out of chlorpyrifos inventories and existing stocks. Gharda explained that six months would not be a meaningful time period, given that it would largely overlap with the off season for chlorpyrifos use and because its customers purchase product at least one to two years in advance of each growing season. Following this call, Gharda followed up in writing to offer voluntary cancellation of additional 10X uses and eliminate aerial and air blast methods of application; Gharda urged EPA to extend the phase out periods for formulation, distribution, and use, to allow for an orderly exhaustion of inventories and to minimize potentially catastrophic economic losses to Gharda and others in the supply chain, at a minimum until July 2022 to cover part of the next growing season. *See* Exhibit H. After this exchange, EPA indicated that it was "very close" to reaching final agreement with Gharda.

33. At EPA's request, Gharda had a further call with EPA and its counsel on July 14, 2021, during which EPA indicated that Gharda's proposal was under review by EPA leadership but that EPA hoped to have a final response within a week. EPA indicated that it would likely need a voluntary cancellation letter from Gharda quickly, to reference the voluntary cancellation in the published final rule. During the call, EPA, for the first time, indicated that its leadership believed that import tolerances would also need to be voluntarily cancelled. EPA could not

explain the basis for this last-minute request, given that import tolerances do not raise drinking water or occupational concerns, and given that the PID did not identify any dietary (non-drinking water) risks associated with chlorpyrifos or import tolerances, even with the retention of the 10X safety factor. Nevertheless, believing it was very close to reaching final agreement with EPA and to avoid derailing months of negotiations, Gharda submitted a proposal to EPA for the cancellation of certain import tolerances. *See* Exhibit I. Gharda followed up asking EPA to consider its points concerning import tolerances, but stressed that it did not want the import tolerance issue to stand in the way of resolving voluntary cancellation of uses pursuant to the terms discussed, as summarized in Gharda's July 6 email. *See* Exhibit J. EPA responded stating that it appreciated Gharda's engagement on this challenging issue. *See id.*

34. Following this submission and response, Gharda heard nothing further from EPA for weeks.

35. Growing increasingly concerned as the court deadline for EPA to issue a final rule was approaching, Gharda requested a meeting with EPA leadership. After Gharda's repeated outreach, EPA finally allowed Gharda to have a twenty-five-minute meeting with Assistant Administrator Michal Freedhoff and others from EPA on August 16, 2021. During the meeting, Gharda reiterated its commitment to voluntarily cancel uses as set forth above, urged EPA to make a decision consistent with science and law, and again stressed the major supply chain disruptions and catastrophic losses that would result from a revocation of tolerances with immediate effect. EPA was silent during this meeting, indicating only that it was willing to "work collaboratively" with Gharda going forward.

36. The next day after its meeting with EPA leadership, Gharda discovered a posting on EPA's website announcing the August 2021 revocation of all tolerances for chlorpyrifos,

which Gharda also discovered was posted days **before** its August 16 meeting with EPA leadership. When Gharda reached out to senior career leadership at EPA about the posting, EPA apologized for the posting and immediately removed it, but confirmed that the final rule would be consistent with the website posting. EPA indicated that there would be "elbow room" on timing of the final rule's implementation.

37. The next day, the EPA Final Rule was announced. In the Final Rule, EPA stated that it was revoking all food use tolerances for chlorpyrifos, as "[b]ased on the currently available data and taking into consideration the currently registered uses for chlorpyrifos," it was unable to make a safety finding under the FFDCA. 86 Fed. Red. 48,315. The Final Rule stated that revocations of the tolerances would take effect on February 28, 2022, six months from the date of publication, to comply with international trade obligations. *Id*. at 48,334.

38. On August 18, 2021, the day the Final Rule was announced, EPA held a public briefing session regarding the Final Rule. EPA invited stakeholders to submit questions to EPA regarding about the Final Rule.

39. Following EPA's public briefing, Gharda and others submitted questions to EPA, concerning the Final Rule's scope, applicability, timing for implementation, and harmonization with FIFRA. Gharda specifically asked whether EPA would consider mitigation in light of Gharda's commitment to accept label modifications limiting use of chlorpyrifos to the select crop uses in select regions EPA determined in the PID were safe and what additional mitigation EPA believed it needed to act on its safety finding. Among other questions, Gharda also asked whether EPA had reviewed or was willing to consider the 2020 Corteva drinking water study.

40. On September 20, 2021, over a month after the Final Rule was announced, EPA posted responses to "Frequent Questions about the Chlorpyrifos 2021 Final Rule" ("FAQs") on

its website,[2] and responded directly to Gharda's questions that were not addressed in the FAQs. *See* Exhibit K. EPA's responses did not appear to allow any "elbow room" or opportunities to "work collaboratively" on the Rule's timing and implementation, but instead directed interested parties to submit objections. EPA also did not respond to Gharda's question concerning label modifications consistent with the Agency's safety finding, and indicated that "due to time constraints" it was unable "to conduct additional scientific analysis beyond what was already available at the time of the court ruling." *Id.*

EPA's Final Rule Has Caused and Will Continue to Cause Significant Harm

41. The Final Rule has caused and will continue to cause significant and irreparable harm to Gharda and others in the agricultural value chain. This is particularly so as to the six-month period for the Final Rule's implementation. The current 2021 growing season has essentially ended, and chlorpyrifos would not be used until the next growing season beginning approximately in April 2022. Thus, the six month period provided in the Final Rule beginning in August 2021 and running through February 2022 is effectively meaningless and allows no time for Gharda, distributors, and growers to phase out and exhaust existing inventories and that will result in the needless waste of safe and wholesome food. The realities of the current supply chain were pointed out to EPA in discussions leading up to the Final Rule.

42. As a result of Gharda's increased production to meet market demand after Corteva's exit from the market, Gharda has a significant volume of raw materials and U.S. labeled product in inventory. Without the ability to formulate, distribute, and sell these products, Gharda will suffer Redacted - CBI economic losses, to say nothing of the nearly Redacted - CBI

[2] https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule#question-2.

loss in its investment in chlorpyrifos and lost future sales of chlorpyrifos products in the U.S. of approximately Redacted - CBI annually. In total, the economic losses Gharda will face if the Final Rule is not reversed or rescinded will be catastrophic.

43. Beyond these economic losses, Gharda has suffered and will continue to suffer significant reputational harm as a result of EPA's arbitrary action against chlorpyrifos. By revoking all tolerances, EPA has directly attacked the safety of chlorpyrifos in the eyes of growers, processors, and consumers, and the credibility of Gharda in selling and distributing chlorpyrifos products. EPA has done this despite a finding by its own expert scientists that a subset of eleven high-benefit chlorpyrifos uses in certain geographic areas are safe, and in disregard of written commitments provided to EPA by Gharda ***prior to the Final Rule*** to modify Gharda's label consistent with EPA's safety finding in its PID.

44. EPA's revocation action has and will continue to strain Gharda's relationships with its customers, who distribute its products to suppliers and end users. Indeed, during its months of negotiations with EPA, Gharda assured its customers that it was working cooperatively with EPA to reach agreement that would allow for many continued agricultural uses. Given EPA's scientific assessment in the PID which provided a clear scientific record on which to retain at least the 10X chlorpyrifos uses, neither Gharda nor its customers expected that EPA would take draconian action to eliminate all uses. EPA's abrupt departure from its own scientific findings has cast doubt on Gharda's credibility and resulted in a loss of customer goodwill.

45. In addition to the immediate and irreparable harm caused to Gharda by EPA's action, EPA's revocation action could create long-term irreparable harm to Gharda because of the stigma attached to the unfounded public statements by EPA that its action was taken "to

ensure children, farmworkers, and all people are protected from the potentially dangerous consequences of this pesticide," and "follow[s] the science and put[s] health and safety first." https://www.epa.gov/newsreleases/epa-takes-action-address-risk-chlorpyrifos-and-protect-childrens-health. There is no scientific basis for these statements, which are in fact directly at odds with EPA's Final Rule and the scientific findings set forth in the PID. *See, e.g.*, 86 Fed. Reg. at 48,324 (EPA "remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported by [epidemiology studies reporting neurodevelopmental impacts in children]"); *id.* at 48,335 ("EPA has not conducted a formal EJ analysis for this rule"); PID at 10 ("the science addressing neurodevelopmental effects remains unresolved").

46. The stigma attached to EPA's public statements not only has the potential to cause ill-will against Gharda by customers, consumers, and the public, but will also adversely affect Gharda's ability to meet the needs of growers for effective pesticide products, compounding the ill-will against Gharda. Customers who abandon Gharda products now because of the Agency's action may not return to using products produced by Gharda even in the event of a final adjudication in Gharda's favor. Gharda may thus permanently lose a significant portion of its market share. Moreover, EPA's actions may trigger other federal or state regulatory requirements or bans, as well as restrictions by foreign governments, who look to EPA as the gold standard for making regulatory decisions based on science.

47. Losses from an immediate removal of chlorpyrifos from the U.S. market would not be borne by Gharda alone. It will also cause significant financial hardship to distributors and growers who invested substantial sums in reliance on the registration in products they are no longer able to sell or use. Most distributors purchase products from Gharda at least a year in advance, and as a result have significant product on hand in order to meet market needs and often

fluctuating demand by U.S. growers. Gharda has been specifically informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI. Growers, for their part, not only face a lost investment in unusable product but also must find alternative, sometimes more expensive alternative products or risk significant crop losses. In total the volume of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers is estimated to be valued at Redacted - CBI.

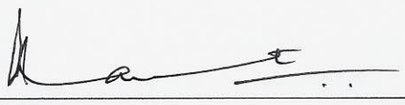
48. Commodity traders and other holders of food and feed with detectable chlorpyrifos residues face significant uncertainty, as it may be practically impossible to demonstrate that the residues result from a lawful application, particularly in the case of finished food and feed product with extended shelf lives. This confusion could result in the unnecessary waste of otherwise safe and nutritious food and feed.

49. Moreover, by insisting on giving immediate effect to the revocation actions, EPA has caused confusion on the part of the public with respect to the safety of dozens of commodities on which chlorpyrifos may legally be used.

50. For these reasons, and those set forth in its Objections, Gharda believes that the Final Rule should be summarily reversed or, at a minimum, stayed pending administrative and, potentially, judicial review of the objections of Gharda, growers, grower groups, and other adversely affected stakeholders.

I declare that the foregoing is true and correct to the best of my knowledge.

Dated: October 22, 2021



Ram Seethapathi
President

Appendix A
List of Comments and Other Submissions to EPA Gharda has Supported Through the Chlorpyrifos Industry Task Force

1. DAS Response to 2014 Revised Human Health Risk Assessment for Chlorpyrifos, (Apr. 29, 2015), EPA-HQ-OPP-2015-0653-0214;
2. Decl. of C. Burns in support of DAS Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for Organophosphate Pesticides, (Dec. 22, 2015), EPA-HQ-OPP-2015-0653-0230 (submitted to docket EPA-HQ-OPP-2010-0119);
3. DAS Response to EPA's Proposed Rule to Revoke Chlorpyrifos Tolerances (including all references and appendices), (Jan. 4, 2016), EPA-HQ-OPP-2015-0653-0386;
4. DAS Legal and Policy Comments in Response to EPA's Proposed Rule to Revoke Tolerances for Chlorpyrifos, (Jan. 5, 2016), EPA-HQ-OPP-2015-0653-0266;
5. DAS Response to Chlorpyrifos-Methyl Human Health Draft Risk Assessment, (Sept. 15, 2015), EPA-HQ-OPP-2010-0119-0044;
6. DAS Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for Organophosphate Pesticides and (ii) EPA's Chlorpyrifos-Methyl Human Health Draft Risk Assessment, (Feb. 19, 2016), EPA-HQ-OPP-2010-0119-0033;
7. DAS Comments on 2016 Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos, (Jan. 17, 2017), EPA-HQ-OPP-2015-0653-0651;
8. Decl. of C. Burns in support of DAS Comments on EPA's Response to Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides (Dec. 29, 2016), EPA-HQ-OPP-2008-0316-0071, (submitted to docket EPA-HQ-OPP-2010-0119);

9. DAS Legal and Policy Comments on (i) EPA's Response to Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides; (ii) Response to Occupational and Residential Exposure-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments; and (iii) Response to Dietary-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments, (July 24, 2017) (submitted to docket EPA-HQ-OPP-2010-0119);
10. DAS Response to Objections to EPA's Denial of Petition to Revoke Tolerances and Cancel Registrations for Chlorpyrifos (and supporting Declarations), (Aug. 27, 2018) (submitted to docket EPA-HQ-OPP-2007-1005-0526);
11. Br. of Amicus Curiae Dow AgroSciences in Supp. of EPA, LULAC v. Wheeler, Nos. 19-71979, 19-71982 (9th Cir. Mar. 6, 2020), ECF No. 53-2;
12. D. Juberg and J. Driver, A Review of Recent Studies - Red Blood Cell Cholinesterase Inhibition as a Point of Departure for Regulation of Chlorpyrifos is Protective Against Neurodevelopmental Toxicity, (June 17, 2020) ("DAS Review of Recent Studies");
13. D. Juberg and J. Driver, Scientific Bases and Perspectives on Uncertainty and Safety Factors for Assessing Risks Associated with Human Chlorpyrifos Exposures, (June 17, 2020) ("DAS Submission on Uncertainty and Safety Factors");
14. A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days, MRID 51392601, submitted by Corteva Agriscience, and
15. Corteva Agriscience's Comments on Chlorpyrifos Proposed Interim Registration Review Decision (Feb. 2, 2021).

EXHIBIT A

Gharda Chemicals International, Inc.

April 19, 2021

Dana Friedman
Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460
friedman.dana@epa.gov

Via Email

Re: Gharda Chemicals International, Inc.'s Registration of Chlorpyrifos

Dear Ms. Friedman,

On behalf of Gharda Chemicals, Inc. ("Gharda"), I look forward to our April 20, 2021 meeting with the U.S. Environmental Protection Agency ("EPA" or the "Agency") to discuss Gharda's registration of chlorpyrifos, a critically important U.S. agricultural tool. Gharda submits this letter in response to the Agency's request that Gharda confirm in writing in advance of the meeting Gharda's agreement to voluntarily cancel numerous currently approved uses of chlorpyrifos.

As set forth below, Gharda believes that such a curtailment of currently approved uses on such a rushed timetable is not reasonable. Gharda is, however, willing to have discussions with the Agency on a reasonable timetable regarding the phase-out of several uses of chlorpyrifos, under appropriate terms and conditions.

Gharda understands that the new Administration is prioritizing its review of certain products, including chlorpyrifos. Respectfully, however, the timetable EPA is asking Gharda to meet is not reasonable and represents a rush to judgment, particularly when the Agency has not completed its review of comments on its Proposed Interim Decision (PID) for chlorpyrifos submitted by Gharda and other stakeholders, or an important recent drinking water study submitted to the Agency by Corteva Agriscience (MRID 51392601). Gharda is especially concerned that EPA would entertain the elimination of certain highly beneficial uses like corn, before examining public comments and recent additional scientific evidence supporting both EPA's current regulatory standard for assessing human health risks of chlorpyrifos and a Food Quality Protection Act safety factor of 1X. *See* Gharda's Comments on PID, EPA-HQ-OPP-2008-0850-0999. EPA's new Administrator has said publicly that the Agency's decisions

concerning chlorpyrifos will be driven by science and the rule of law. Gharda thus trusts and expects that EPA will afford stakeholders appropriate due process and consider the full weight of the scientific evidence before taking action that would eliminate important uses, with significant disruptive consequences.

Gharda is nevertheless willing to discuss with EPA some possible modifications to its registration label for chlorpyrifos that would allow for a continuation of crucial agricultural uses, while being responsive to the Agency's request. For example, Gharda may be willing to agree to elimination of the following crop uses: caneberry, kiwifruit, cherimoya, banana, fig, feijoa, date, calamondin, chironja, citron, pummelo, tangor, barley, pepper, filberts, tobacco, spearmint, and peppermint. Gharda may also be willing to agree to elimination of the following non-crop uses: crack and crevice/void/general outdoor, golf course turf, lawncare (commercial), wood treatment, wide area use, foundation/walls, perimeter, and cattle ear-tag. Gharda is also willing to discuss potential geographic restrictions on crop uses and other risk mitigation measures. Gharda believes that, where possible, a phased implementation of any label modifications should be employed, to avoid negatively impacting growers and others in the agricultural value chain.

While Gharda is committed to engaging in a dialogue with EPA on these issues, Gharda is not currently able to meet the rushed timetable the Agency has presented. Chlorpyrifos comprises a significant portion of our U.S. agrochemical business, on which many jobs depend. Chlorpyrifos is also a vitally important pest management tool; it is often the first tool growers employ to control new or unknown insect pests and, as the Agency knows, for some destructive insect pests it is growers' last line of defense. Indeed, at a time when our growers need as many tools in their tool box as possible to adapt to the adverse effects of climate change, reducing their ability to use such a highly efficacious pesticide as chlorpyrifos would be an unfortunate action for the federal government to take. Gharda thus needs additional time to evaluate different options for label modifications and their potential impacts on Gharda's business, its customers, and the agricultural economy.

We thank you in advance for your consideration of the concerns we have outlined and look forward to a productive meeting.

Respectfully submitted,

Ram Seethapathi
President, Gharda Chemicals International, Inc.

EXHIBIT B

Gharda Chemicals International, Inc.

May 12, 2021

Dana Friedman
Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460
friedman.dana@epa.gov

Via Email

Re: Gharda Chemicals International, Inc.'s Registration of Chlorpyrifos

Dear Ms. Friedman,

On behalf of Gharda Chemicals, Inc. ("Gharda"), I write in follow up to our discussions concerning the request by the U.S. Environmental Protection Agency ("EPA" or the "Agency") that Gharda agree to a voluntary cancellation of certain currently approved uses of chlorpyrifos.

It continues to be Gharda's position that all currently approved uses of chlorpyrifos are strongly supported by scientific data, including the application of a 1X safety factor pursuant to the Food Quality Protection Act ("FQPA"). However, Gharda understands that the Agency is under time constraints to act with respect to chlorpyrifos tolerances in light of the recent decision by the U.S. Court of Appeals for the Ninth Circuit in *League of United Latin American Citizens, et al. v. Michael Regan, et al*, consolidated Case Nos. 19-71979, 19-71982 ("*LULAC II*"). Gharda believes the decision is flawed and remains hopeful that EPA will seek rehearing of and/or appeal the decision. Gharda is nevertheless willing to work with EPA to negotiate the voluntary cancellation of many currently approved uses of chlorpyrifos on mutually acceptable terms and in a manner that minimizes disruption on growers and other users.

In particular, Gharda is willing to negotiate and execute an agreement with EPA containing at least the following key terms:

- Uses remain in place for the 11 high-benefit agricultural crops in certain regions that the Agency listed in its 2020 Proposed Interim Decision (PID) for chlorpyrifos as uses, together with their associated tolerances, that will not pose potential risks of concerns with an FQPA safety factor of 10X; some of the geographic restrictions set forth in the PID as to the 11 crops to be further discussed;

- Existing uses for some additional key crops, specifically corn, mint, and grapes, would remain in place in certain regions together with their associated tolerances; Gharda is willing to negotiate geographic restrictions and other label modifications and risk mitigation measures that would allow for a continuation of these critical agricultural uses;
- Gharda would agree to a voluntary cancellation of all other agricultural uses of chlorpyrifos pursuant to scheduled phase-outs;
- Gharda's production, sale, and distribution of chlorpyrifos products permitting use on the voluntarily cancelled uses would be allowed as follows;
    - through December 31, 2022 for Caneberry, Kiwifruit, Carrot (Grown for seed), Ginseng, Rutabagas, Cherimoya, Banana, Fig, Feijoa, Date, Calamondin, Chironja, Citron, Kumquat, Mandarin (tangerine), Pummelo, Satsuma mandarin, Tangelo, Tangor, Barley, Triticale, Cucumber, Pumpkin, Leek, Tomatoes, Pepper, Nectarines, Plum, Plums/Prunes, Filberts, Tobacco, Sugarcane, Spearmint, Peppermint, Crack and Crevice/Void/General Outdoor, Golf Courses Turf, Lawncare (Commercial), Trash Storage Areas, Wood Treatment, Wide Area Use, Foundation/Walls, Perimeter, Nursery (Conifer Plantations, Forest Plantings, Forest Trees, Cottonwood/Poplar Plantations, Nursery Stock, Ornamental/Shade Trees, Ornamental Nonflowering Plants, Ornamental Woody Shrubs), Perennial Grass Seed Crops, Cattle Ear-Tag;
    - through December 31, 2024 for Blueberry, Cranberries, Potatoes, Sweet Potato, Clover (Grown for Seed), Oats, Grass Forage, Fodder, Hay, Legume Vegetables (Succulent (All), Dried (All)), Peas (Seed Treatment), Cherry (sweet), Pears, Broccoli, Broccoli (cavalo, Chinese and raab), Brussels sprouts, Cabbage, Cabbage (Chinese), Cauliflower, Collards, Kale, Kohlrabi, Mizuna, Mustard greens, Mustard spinach, Turnips, Radishes, Rape greens, Nursery (Christmas Tree Plantations);
    - through December 31, 2026 for Canola, Sorghum (Milo), Sunflower, Onions, Almonds, Pecans, Walnuts, Tree/Nut (pecan orchard floors), Tree/Nut (walnut orchard floors), Peanuts.
- Appropriate existing stocks orders and applicable label changes would take effect after each of the scheduled phase-outs for the voluntarily cancelled uses;
- All import tolerances for chlorpyrifos would be retained;
- Gharda reserves the right to withdraw from the written agreement in the event that the Ninth Circuit grants panel rehearing or rehearing *en banc* in *LULAC II* or the U.S. Supreme Court grants *certiorari* in that case;
- Gharda would reserve all rights to seek approval of new or previously approved uses of chlorpyrifos in the future, in accordance with the requirements of the Federal Insecticide, Fungicide, and Rodenticide Act; and,
- Nothing in the written agreement between EPA and Gharda would constitute a finding or admission that the voluntarily cancelled uses present any neurodevelopmental or other human health risks.

Gharda is prepared to cooperate with the Agency and looks forward to a productive discussion with EPA concerning these issues.

Respectfully submitted,

Ram Seethapathi
President, Gharda Chemicals International, Inc.

EXHIBIT C

Gharda Chemicals International, Inc.

June 7, 2021

Dana Friedman
Branch Chief
Risk Management and Implementation Branch I
Pesticide Re-Evaluation Division
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave, NW
Washington, DC 20460
friedman.dana@epa.gov

Via Email

Re: Gharda Chemicals International, Inc.'s Registration of Chlorpyrifos

Dear Ms. Friedman,

On behalf of Gharda Chemicals, Inc. ("Gharda"), I write in follow up to our discussions concerning the request by the U.S. Environmental Protection Agency ("EPA" or the "Agency") that Gharda agree to a voluntary cancellation of certain currently approved uses of chlorpyrifos.

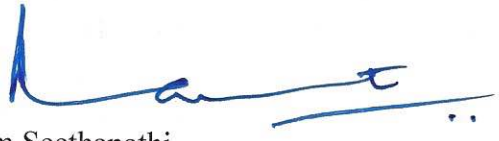
Gharda understands that the Agency believes it has insufficient time to complete further analyses at this time and must act immediately with respect to chlorpyrifos tolerances under the recent decision by the U.S. Court of Appeals for the Ninth Circuit in *League of United Latin American Citizens, et al. v. Michael Regan, et al*, consolidated Case Nos. 19-71979, 19-71982 ("*LULAC II*"). Gharda believes that the *LULAC II* decision is flawed and that a Food Quality Protection Act ("FQPA") safety factor of 1X and point of departure based on 10% red blood cell cholinesterase inhibition are strongly supported by the scientific record. Gharda is nevertheless willing to continue to work with EPA to negotiate the voluntary cancellation of many currently approved uses of chlorpyrifos on mutually acceptable terms and in a manner that minimizes disruption on growers and other users.

Accordingly, Gharda commits to voluntarily cancel all currently approved agricultural uses of chlorpyrifos other than uses for the 11 high-benefit agricultural crops in select regions that the Agency has identified on pages 40–41 of its 2020 Proposed Interim Decision (PID) for chlorpyrifos (EPA-HQ-OPP-2008-0850) (those 11 high-benefit agricultural crops are alfalfa, apple, asparagus, cherry (tart), citrus, cotton, peach, soybean, strawberry, sugar beet, wheat (spring and winter)). Gharda's agreement to voluntarily cancel uses is subject to the following conditions:

- Uses, together with their associated tolerances, for the 11-high benefit agricultural crops will remain in place in the select regions, as outlined on pages 40–41 of the PID, as well as in Texas for cotton;
- EPA and Gharda reach mutually agreeable provisions that will (i) allow finished technical product in Gharda's warehouse at its manufacturing facility outside of the United States and in transit from the manufacturing facility that have not yet cleared the U.S. Customs and Border Protection and EPA import approval process at the time of the order for voluntarily cancelled uses to be processed and sold in the United States for all currently registered uses, and (ii) allow product in Gharda's possession in the United States at the time of the order for voluntarily cancelled uses to be processed and sold for all currently registered uses;
- EPA and Gharda reach mutually agreeable label revisions and approval process and timing that mitigate disruption on growers and other users and are consistent with the agreement in the previous bullet;
- EPA and Gharda reach mutually agreeable existing stocks provisions that mitigate disruption on growers and other users;
- All current import tolerances for chlorpyrifos are retained;
- Gharda reserves all rights to seek approval of new or previously approved uses of chlorpyrifos in the future, in accordance with the requirements of the Federal Insecticide, Fungicide, and Rodenticide Act;
- Gharda and EPA agree that products (including commodity products like corn and soybean) lawfully treated with chlorpyrifos prior to a final cancellation order taking effect will be permitted to clear the channels of trade, pursuant to 21 U.S.C. Section 346a(l)(5);
- Gharda and EPA agree that Gharda's voluntary cancellation of uses would not constitute a finding or admission that the voluntarily cancelled uses present any neurodevelopmental or other human health risks; and,
- Gharda reserves the right to withdraw from the voluntary cancellation of uses in the event that the Ninth Circuit grants panel rehearing or rehearing *en banc* in *LULAC II* or the U.S. Supreme Court grants *certiorari* in that case.

Gharda looks forward to working with the Agency on next steps.

Respectfully submitted,



Ram Seethapathi
President, Gharda Chemicals International, Inc.

EXHIBIT D

[redacted]

\f0From: Biggio, Patricia <biggio.patricia@epa.gov>
Sent: Tuesday, June 8, 2021 2:42 PM
To: Friedman, Dana; Ram Seethapathi
Cc: Pyne, Jaclyn; Feitel, Alexandra
Subject: RE: Chlorpyrifos: Gharda letter

\f0

\f0

Hi Ram,

Thank you for your letter. We see that Gharda has requested to maintain use of chlorpyrifos on cotton in Texas. The PID indicated that if cotton were maintained, it could be used in AL, FL, GA, NC, SC, and VA. Unfortunately, Texas would not be an option for this use based on the revised drinking water assessment which took into account the US watershed regions as part of the refined assessment.

We would like to see if Gharda is prepared to move forward with discussing voluntary use cancellations. If so, we can look to schedule a call that will include EPA counsel. We are considering the following dates for existing stocks:

- Technical grade active ingredient: Phase out most uses by the end of 2021; allow until the end of 2022 (12 to 18 months) for the remaining uses
- End-use products: 12 to 18 months from the technical registrants for sale/distribution of products
- End users, growers: Until exhausted

Please let us know if you are available for a call in the next week or so.

Thank you,

Trish

From: Friedman, Dana <Friedman.Dana@epa.gov>
Sent: Tuesday, June 8, 2021 6:40 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: RE: Chlorpyrifos: Gharda letter

Thanks Ram. We'll take a look today and be back in touch with you as soon as possible.

From: Ram Seethapathi <sramanathan@gharda.com>
Sent: Monday, June 7, 2021 5:49 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: Chlorpyrifos: Gharda letter

Dear Ms. Friedman,

Please see attached letter from Gharda based on our continued discussions on chlorpyrifos.

Thanks very much for giving time extension until today to send this letter. Appreciate your help.

Look forward to hearing from you further in this regard.

Thanks and best regards,

Ram Seethapathi.

President

Gharda Chemicals International Inc.,

760, Newtown Yardley Road, Suite 110,

Newtown, PA 18940

Ph: 215-968-9474

Mob: 215-791-0956

EXHIBIT E

[redacted]

From: Ram Seethapathi <sramanathan@gharda.com>
te: Friday, June 11, 2021 at :27 PM
To: Biggio, Patricia <biggio.patricia@epa.gov>, Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: Re: Chlorpyrifos: Gharda letter

Hi Trish,

Thanks for your email below.

I have sent an email to Dana ust now seeking 10 minutes of her time to get answers for some follow up questions.

As soon as we connect, meeting with your attorneys can be scheduled, as desired by you.

Have a great weekend.

Best Regards,

Ram

From: Biggio, Patricia <biggio.patricia@epa.gov>
te: Tuesday, June 8, 2021 at 2:42 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>, Ram Seethapathi <sramanathan@gharda.com>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: RE: Chlorpyrifos: Gharda letter

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Trish

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Sent: Tuesday, June 8, 2021 6:40 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: RE: Chlorpyrifos: Gharda letter

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From: Ram Seethapathi <sramanathan@gharda.com>

Sent: Monday, June 7, 2021 5:49 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: Chlorpyrifos: Gharda letter

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Thanks and best regards,

Ram Seethapathi,

President

Gharda Chemicals International Inc.,

760, Newtown Yardley Road, Suite 110,

Newtown, PA 18940

Ph: 215-968-9474

Mob: 215-791-0956

EXHIBIT F

[redacted]

From: Biggio, Patricia <biggio.patricia@epa.gov>
Sent: Thursday, June 24, 2021 6:18 PM
To: Ram Seethapathi
Cc: Friedman, Dana; Pyne, Jaclyn; Feitel, Alexandra
Subject: Chlorpyrifos discussion notes

Dear Ram,

Thank you for your time this afternoon. We are writing to confirm the uses that Gharda has agreed upon for retention following our discussions over the past few weeks and our call this afternoon:

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Cotton and strawberry will be phased out over two years (until 202)
- Aerial application will be phased out over 2 years (until 202)
- Provisions for existing stocks:
    - Technical products may be sold or distributed until 12/ 1/2021
    - End-use products may be sold or distributed until 12/ 1/2022

Please let me know if there are any questions.

Thank you,

Trish

Patricia Biggio

Chemical Review Manager

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

Phone: 70 - 47-0547

biggio.patricia@epa.gov

EXHIBIT G

[redacted]

From: Ram Seethapathi <sramanathan@gharda.com>
te: Friday, June 25, 2021 at 5:25 PM
To: Biggio, Patricia <biggio.patricia@epa.gov>
Cc: Friedman, Dana <Friedman.Dana@epa.gov>, Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: Re: Chlorpyrifos discussion notes

Dear Trish,

Thank you for your email and telephone conversation this morning. In order to bring more clarity to your email and my response, the following terms are consistent with the group discussions yesterday (6/24/21):

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Provisions for the exhaustion of remaining inventories:
    - Technical products for current label uses brought into the United States by 12/ 1/2021 can be sold or distributed by Gharda through that date
    - End-use products for the current label uses may be formulated, packaged, sold or distributed by Gharda and others until 12/ 1/2022
- Provisions for existing stocks:
    - Existing stocks for the current label uses exhausted by distributors, growers and other users by 12/ 1/202
- Aerial application will be voluntarily removed from the label by 12/ 1/202
    - Gharda can manufacture, sell, and distribute for the 11 high-benefit crops set forth in Table 10 of the December 2020 PID with aerial application as to technical and end use products through 12/ 1/2
    - Entities other than Gharda in the channels of trade can sell or distribute chlorpyrifos products for the 11 high-benefit crops with aerial application to be further discussed with Gharda's preference through exhaustion
    - Growers/end users can use chlorpyrifos products for the 11 high-benefit crops with aerial application to be further discussed with Gharda's preference through exhaustion
- Cotton and strawberry will be voluntarily removed from label by 12/ 1/202
    - Time periods for existing stocks orders and label changes to be addressed for the phased-out uses on cotton and strawberry

With respect to import tolerances, Gharda has considered and believes that all import tolerances should be retained, as previously agreed. In addition, as set forth in our previous correspondence

- Terms will be set forth in a separate, written agreement between Gharda and EPA
- Gharda reserves the right to withdraw from the written agreement in the event that the U.S. Supreme Court grants certiorari in the *LULAC II* case
- Gharda would reserve all rights to seek approval of new or previously approved uses of chlorpyrifos in the future, in accordance with FIFRA
- Nothing in the written agreement between EPA and Gharda would constitute a finding or admission that the voluntarily cancelled uses or method of application present any neurodevelopmental or other human health risks or ecological risks.

Gharda looks forward to working with the Agency to finali e the above terms.

Let me know if you have any questions.

Have a great weekend.

Best regards,

Ram

From: Ram Seethapathi <sramanathan@gharda.com>
te: Friday, June 25, 2021 at 9:19 AM
To: Biggio, Patricia <biggio.patricia@epa.gov>
Cc: Friedman, Dana <Friedman.Dana@epa.gov>, Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: FW: Chlorpyrifos discussion notes

Hi Trish, good morning again. Thanks for being available when I called ust now.

As desired, I am showing some of my immediate observations from your email, marked in RED in the body of your email. For want of time I have done this

Thanks regards,

Ram

From: Biggio, Patricia <biggio.patricia@epa.gov>
te: Friday, June 25, 2021 at 8:01 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Friedman, Dana <Friedman.Dana@epa.gov>, Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: RE: Chlorpyrifos discussion notes

Hi Ram,

We will be meeting internally this morning and would like to know if we can present where Gharda stands using the list below. Please let us know by 9:00 this morning or let me know if you would like a quick call to discuss.

Thank you,

Trish

From: Biggio, Patricia
Sent: Thursday, June 24, 2021 6:18 PM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Friedman, Dana <Friedman.Dana@epa.gov>; Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>; Feitel, Alexandra <feitel.alexandra@epa.gov>
Subject: Chlorpyrifos discussion notes

Dear Ram,

Thank you for your time this afternoon. We are writing to confirm the uses that Gharda has agreed upon for retention following our discussions over the past few weeks and our call this afternoon:

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Cotton and strawberry will be phased out/eleminated ~~over~~ in two years (~~until~~ by end 202): Time frame to be defined for Inventory to be cleared in channel and farmer
- Aerial application will be eliminated ~~phased out~~ on the label in ~~over~~ 2 years (~~until~~ by end 202): Time frame to be defined for Inventory to be cleared in channel and farmers
- Provisions for existing stocks:
    - Technical products should be in the country by 12/ 1/2021 and may be packaged for end use with current labels or sold or distributed until 12/ 1/2021
    - Such End-use products may be sold or distributed by Gharda until 12/ 1/2022
    - We discussed about a period for channel to clear the inventory and farmers to use product: Ask was 18 months but you have not yet decided on this.
- Prior letters

Import tolerances and some others in our prior letter: We have not discussed your email internally yet and I think I covered most and revert soon if there are any omissions:

Thanks for our good faith negotiations over the last few weeks and looking forward to get confirmation from you.

Please let me know if there are any questions.

Thank you,

Trish

Patricia Biggio

Chemical Review Manager

Pesticide Re-evaluation Division

Office of Pesticide Programs, EPA

Phone: 70 - 47-0547

biggio.patricia@epa.gov

EXHIBIT H

[redacted]

From: Friedman, Dana <Friedman.Dana@epa.gov>
Sent: Tuesday, July 6, 2021 at :50 PM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: RE: Chlorpyrifos

\cbpat5CAUTION: This email originated from outside of the organi ation. Do not click links or open attachments unless you recogni e the sender and know the content is safe.

Thanks Ram, I appreciate your quick turnaround on this after our conversation at noon today. We'll take this to our senior leadership and will let you know what we hear.

Many thanks,

Dana

Dana L. Friedman

Chief, Risk Management and Implementation Branch 1

Pesticide Re-Evaluation Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

70 - 47-8827

From: Ram Seethapathi <sramanathan@gharda.com>
Sent: Tuesday, July 6, 2021 6:06 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: Chlorpyrifos

Dana

I am following up our discussion today with this summary of Gharda's position:

Gharda is willing to accept voluntary cancellation of all 1 crop uses as set forth in EPA's December 2020 PID

Gharda is willing to accept voluntary cancellation of strawberry, asparagus, cherry (tart) and cotton (from EPA's 10 list in the PID), but asks that the Agency reconsider allowing retention of cotton.

Gharda is willing to accept voluntary cancellation of the aerial method of application for the 11 high-benefit crops set forth in Table 10 of the PID

Gharda is willing to accept voluntary cancellation of the air blast method of application for tree fruit crops (apple, citrus, peach)

EPA will allow for continued use on alfalfa, soybean, sugar beet, wheat (summer and winter), apple, citrus and peach in select states as outlined in the December 2020 PID.

In return for Gharda agreeing for all of the foregoing voluntary cancellations, Gharda asks the Agency to (i) allow formulation and distribution of end use products for all current uses through the end of June 2022 instead of February 2022, and (ii) allow use of these products by growers through the end of June 202 instead of August 2022. June 2022 instead of February 2022 is critical for Gharda because this is a very important sale and use period for this product. Additional time for growers to complete use is critical to minimi e disruption and allow for an orderly phase-out of the product for the voluntarily cancelled uses consistent with long-standing EPA policy.

Gharda continues to believe that a written agreement between the parties should be completed in the near future.

Gharda reserves all of its rights as previously communicated.

Thanks very much and I hope Gharda has tried our best to resolve all the concerns expressed by EPA

under given circumstances.

Warm regards,

Ram Seethapathi,

President

Gharda Chemicals International Inc.,

760, Newtown Yardley Road, Suite 110,

Newtown, PA 18940

Ph: 215-968-9474

Mob: 215-791-0956

EXHIBIT I

[redacted]

From: Ram Seethapathi <sramanathan@gharda.com>
te: Thursday, July 15, 2021 at 6:12 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: Chlorpyrifos

Hi Dana,

As agreed, I am responding to our discussion yesterday about import tolerances for chlorpyrifos. Gharda continues to ask EPA to consider the points raised during our discussion and in my email message to you subsequent to our discussion, but does not want the import tolerance issue to stand in the way of resolving this matter pursuant to the other terms that we discussed, as summari ed in my email message dated July 6, 2021.

Thanks and best regards,

Ram Seethapathi,

President

Gharda Chemicals International Inc.,

760, Newtown Yardley Road, Suite 110,

Newtown, PA 18940

Ph: 215-968-9474

Mob: 215-791-0956

EXHIBIT J

[redacted]

From: Friedman, Dana <Friedman.Dana@epa.gov>
te: Friday, July 16, 2021 at 7:24 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: RE: Chlorpyrifos

\cbpat5CAUTION: This email originated from outside of the organi ation. Do not click links or open attachments unless you recogni e the sender and know the content is safe.

Hi Ram,

I ust wanted to confirm our receipt of the below and provide an update that we have forwarded both the import tolerance list and notification of the below for consideration and additional discussion. We do not have an update on when those next internal discussions are set to occur, but should we get any additional updates we can provide, be assured that we will forward that information along as soon as possible.

Again, I really appreciate your continued patience and engagement on this challenging issue.

Regards,

Dana

Dana L. Friedman

Chief, Risk Management and Implementation Branch 1

Pesticide Re-Evaluation Division

Office of Pesticide Programs

U.S. Environmental Protection Agency

From: Ram Seethapathi <sramanathan@gharda.com>
Sent: Thursday, July 15, 2021 6:1 PM
To: Friedman, Dana <Friedman.Dana@epa.gov>
Cc: Biggio, Patricia <biggio.patricia@epa.gov>
Subject: Chlorpyrifos

Hi Dana,

As agreed, I am responding to our discussion yesterday about import tolerances for chlorpyrifos. Gharda continues to ask EPA to consider the points raised during our discussion and in my email message to you subsequent to our discussion, but does not want the import tolerance issue to stand in the way of resolving this matter pursuant to the other terms that we discussed, as summari ed in my email message dated July 6, 2021.

Thanks and best regards,

Ram Seethapathi,

President

Gharda Chemicals International Inc.,

760, Newtown Yardley Road, Suite 110,

Newtown, PA 18940

Ph: 215-968-9474

Mob: 215-791-0956

EXHIBIT K

[redacted]

From: Feitel, Alexandra <feitel.alexandra@epa.gov>
te: Monday, September 20, 2021 at 10:2 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Friedman, Dana <Friedman.Dana@epa.gov>, Grable, Melissa <Grable.Melissa@epa.gov>
Subject: RE: Update on chlorpyrifos rule

i Ram,

Apologies for multiple emails. Gharda s questions on the chlorpyrifos final rule that are not addressed in the FA s are answered below:

Will EPA consider an extension of the effective date of the Final Rule so that existing inventories can be formulated, sold/distributed and used? For how long?
Under FFDCA section 408(g), 21 U.S.C. 46a, any person may file an ob ection to any aspect of this regulation including consideration of an extension of the effective date. Any person may also request a hearing on those ob ections. All ob ections and requests for a hearing must be in writing and must be received by the Hearing Clerk on or before 60 days after the final rule was published in the Federal Register. Please see Section 1C of the final rule for instructions on providing feedback.

What input on the Final Rule does EPA expect to receive from FDA?
EPA has been working closely with FDA on a guidance for treated commodities in the channels of trade. For additional information on channels of trade, please contact the Center for Food Safety and Applied Nutrition at the US FDA (CFSANTradepress@fda.hhs.gov).

Does EPA expect to receive input from the WTO and other sources regarding the effective date of the Final Rule? What is the timing of this anticipated input from the WTO?
The WTO was notified of the Agency's decision on this Final Rule. The Agency will respond to all WTO member comments as they are received.

Has EPA had an opportunity to review the Corteva drinking water study? Is EPA willing to review that study in the near term?
EPA has the Corteva drinking water study in house for review. Due to time constraints, EPA was not able to conduct additional scientific analysis beyond what was already available at the time of the court ruling.

Does this action cover livestock feed as well as food for human consumption?
This action revokes all tolerances, including tolerances for food, feed, and livestock commodities.

-

From: Feitel, Alexandra
Sent: Monday, September 20, 2021 : 4 AM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>; Friedman, Dana <Friedman.Dana@epa.gov>; Grable, Melissa <Grable.Melissa@epa.gov>
Subject: RE: Update on chlorpyrifos rule

Good morning Ram,

The chlorpyrifos FA s were ust posted to the EPA website: https: www.epa.gov ingredients used pesticide products frequent questions about chlorpyrifos 2021 final rule question 1

Please let me know if you have any further questions.

Thank you,
Alex

From: Ram Seethapathi <sramanathan@gharda.com>
Sent: Thursday, August 2 , 2021 : PM
To: Feitel, Alexandra <feitel.alexandra@epa.gov>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>; Friedman, Dana <Friedman.Dana@epa.gov>
Subject: Re: Update on chlorpyrifos rule

i Alexandra,
Thanks for your note below.
ill look forward to the FA s and reach out to you for clarifications.

Thanks and best regards,
Ram

From: Feitel, Alexandra <feitel.alexandra@epa.gov>
te: Thursday, August 2 , 2021 at 2:24 PM
To: Ram Seethapathi <sramanathan@gharda.com>
Cc: Pyne, Jaclyn <Pyne.Jaclyn@epa.gov>, Friedman, Dana <Friedman.Dana@epa.gov>
Subject: Update on chlorpyrifos rule

i Ram,

e were ust notified that the chlorpyrifos final tolerance rule is scheduled to be published in the Federal Register on Monday, August 0th. Additionally, we are finalizing the FA s and will notify you as soon as they are posted to the EPA website. Please let me know if you have any further questions in the meantime.

Thank you,
Alex Feitel

Alexandra Feitel
Chemical Review Manager, Risk Management and Implementation Branch I
Pesticide Re evaluation Division
U.S. EPA Office of Pesticide Programs
0 4 8 1

October 26, 2021

CONTAINS CONFIDENTIAL BUSINESS INFORMATION

VIA UPS

Office of Administrative Law Judges
U.S. Environmental Protection Agency
Attn: Mary Angeles
Mail Code 1900R
1200 Pennsylvania Ave., NW
Washington, D.C. 20460

Donald C. McLean
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Re: Chlorpyrifos Tolerance Revocations (EPA-HQ-OPP-2021-0523, FFDCA-HQ-2021-01)
Gharda Chemicals International, Inc. Submission of Confidential Business Information

Dear Ms. Angeles:

Pursuant to your October 26, 2021 email, enclosed please find two paper copies of Gharda Chemicals International, Inc.'s ("Gharda's") **Business Confidentiality Asserted** Objections to the Final Rule Revoking All Tolerances for Chlorpyrifos, Declaration of Mr. Ram Seethapathi, Declaration of Dr. Richard Reiss, and Petition to Stay the Effective Date of the Revocation of All Tolerances for Chlorpyrifos. Gharda's Confidential Business Information is contained in the Objections to the Final Rule Revoking All Tolerances for Chlorpyrifos, the Declaration of Mr. Ram Seethapathi, and the Petition to Stay the Effective Date of the Revocation of All Tolerances for Chlorpyrifos. Redacted versions of these documents were submitted to the Office of Administrative Law Judges e-filing system and Federal e-Rulemaking Portal on Friday, October 22, 2021.

Thank you in advance for your assistance in the matter. If you have any questions or need any further assistance, please feel free to contact us at donald.mclean@arentfox.com or katie.heilman@arentfox.com.

Sincerely,

Donald C. McLean

Katie Heilman

Enclosures

12647 Olive Boulevard, Suite 410, St. Louis, MO 63141 • PHONE: (314) 576-1770

October 29, 2021

Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Submitted electronically via Office of the Administrative Law Judges E-Filing System and Federal eRulemaking Portal

RE: Formal Written Objections, Request for Evidentiary Hearing, and Request to Stay Tolerance Revocations: Chlorpyrifos (EPA-HQ-OPP-2021-0523)

To Whom It May Concern:

On behalf of the American Soybean Association (ASA), pursuant to the Federal Food, Drug, and Cosmetics Act (FFDCA) section 408(g) (21 U.S.C. 346a), I am writing to file formal objections regarding EPA's final rule issued on August 30, 2021, to revoke all tolerances for the insecticide chlorpyrifos (EPA-HQ-OPP-2021-0523). ASA represents more than 500,000 U.S. soybean farmers on domestic and international policy issues important to the soybean industry and has 26 affiliated state associations representing 30 soybean-producing states.

ASA has numerous concerns with the final rule as published. We believe it is inconsistent with federal statute, the Agency's own record on chlorpyrifos, and sound, science-based and risk-based regulatory practices. We also believe EPA has assumed certain factual errors in the rule that require an evidentiary hearing, which we request below. As a result of these issues and factual errors, we are concerned this rule will result in significant, irreparable harm to soybean growers. To prevent the unavoidable harm that will occur should the rule take effect, we further request EPA stay implementation of the rule until the Agency can formally review and respond to objections raised, including the factual errors ASA is seeking to address in our requested evidentiary hearing.

We would also like to point out that we view the objections listed below as supplemental to those ASA has already raised with other agricultural stakeholders in an objections letter posted to this docket and filed with the Office of the Administrative Law Judges (OALJ) dated October 19, 2021. ASA stands by and reaffirms the objections and stay request raised in that letter and seeks to raise additional concerns with the rule and highlight soybean-specific impacts in this objections letter.

Irreparable Harm to Soybean Producers, the Environment

We are greatly concerned this rule will cause significant, irreparable harm to soybean growers and the environment. Soybean growers rely on chlorpyrifos to control numerous insect pests, but some of the highest-benefit and most critical uses are to control soybean aphids and two-spotted spider mites (TSM) in the Upper Midwest. If left unchecked, these pests can cause up to 60 percent yield loss,[1] and in some cases transmit secondary viruses that can cause further crop damage. Soybean aphids and TSM pose a

[1] Hodgson, Erin. Iowa State University–Extension and Outreach. July 6, 2016. *Spider Mite Injury Confirmed in Soybean*. https://crops.extension.iastate.edu/cropnews/2016/07/spider-mite-injury-confirmed-soybean

serious threat to crops and are notoriously difficult to control. Aphid populations in the Upper Midwest have largely developed resistance to the pyrethroid class of insecticides, and very few control options exist for TSM. Chlorpyrifos is the only chemistry that reliably controls both aphids and TSM. If growers lose access to chlorpyrifos, as would occur from this rule, there is no one-to-one replacement scenario – growers will have to at a minimum spray two active ingredients to control these pests. This rule will increase growers' operational costs by requiring them to purchase more pest control products and will reduce their ability to be good environmental stewards by requiring the application of greater volumes of pesticides in the environment.

In our analysis, the most plausible replacement scenario is the use of dimethoate to control TSM and an application of a 4A mode of action (MOA) chemistry, such as imidacloprid, to control aphids. While dimethoate is registered for use on aphids, its record at controlling this pest is unreliable, therefore we do not believe growers will rely on it for this purpose.[2] While slightly outdated, for the sake of convenience we will use a 2017 analysis on the cost of insect control products to provide a conservative replacement scenario.[3]

Based on this 2017 estimate, a gallon of a chlorpyrifos product would cost a grower $55.00. When assuming a standard application rate of one pint per acre, this results in a cost of $6.88/acre treated. Under this analysis, a common dimethoate product will cost a grower $47.00/gallon. When again assuming a common application rate of one pint per acre, the cost to the grower is $5.88/acre treated. A common imidacloprid product in this analysis will cost a grower $120.00/gallon. When assuming a label-directed application rate of 1.5 ounces/acre, the cost is approximately $1.41/acre treated. Combining the costs of the dimethoate and imidacloprid treatments, a grower could expect to pay $7.29/acre to control these two pests under a scenario without chlorpyrifos – a $0.41 increase per crop acre treated than under the status quo with chlorpyrifos.

Considering EPA estimated in its November 2020 *Revised Benefits of Agricultural Uses of Chlorpyrifos* that U.S. soybean producers use chlorpyrifos on an estimated 3.08 million acres of soybeans annually, this cost is rapidly amplified.[4] When extrapolated, U.S. soybean farmers in this conservative replacement scenario could expect see a $1.26 million annual cost increase to protect their crops. Producers in states like Minnesota, North Dakota, and South Dakota, where these specific pest pressures are higher, will be disproportionally burdened by this impact.

And this scenario would only account for immediate replacement product costs. Growers use a variety of insecticides with multiple biochemical modes of action (MOA) to prevent insect pests from developing resistance to any one chemistry or MOA. By losing access to chlorpyrifos, as would result from this rule, growers will suffer the loss of a vital, effective pest management tool. As a result, growers will have to increasingly rely on the few other remaining chemistries, expediting insect resistance to those other tools and, over time, ultimately resulting in greater crop damage.

Finally, we are very concerned with requirements in the rule that would likely cause growers to lose significant volumes of food and feed product. The rule, after it takes full effect on February 28, 2022, will

---

[2] Potter, Bruce, Robert Koch, Phil Glogoza, Ian MacRae, Janet Knodel. University of Minnesota-Extension. July 31, 2017. "Pyrethroid resistant soybean aphids: What are your control options?" *Minnesota Crop News.* https://blog-crop-news.extension.umn.edu/2017/07/pyrethroid-resistant-soybean-aphids.html

[3] University of Nebraska-Lincoln. N.D. *2017 Approximate Retail Price ($) per Unit of Selected Insecticides for Field Crops.* Accessed October 27, 2021. https://cropwatch.unl.edu/2017-CW-News/2017-documents/insect-management/UNL-EC130-Insecticide-Prices-2017.pdf

[4] Mallampalli, Nikhil, Rebeccah Waterworth, and Derek Berwald. United States Environmental Protection Agency. Office of Chemical Safety and Pollution Prevention. November 18, 2020. *Revised Benefits of Agricultural Uses of Chlorpyrifos (PC# 059101)*.

require holders of food to provide special channels of trade documents verifying any chlorpyrifos residues detected after that date were legal at the time of application and fall below the legal limit under the previously established tolerances. Foods that do not meet these requirements may be found adulterated. However, many soybean producers made chlorpyrifos applications prior to EPA's announcement of this action in August 2020, from which there will be detectable residues. Soybean growers and other producers could not have known at that time that special channels of trade documents would be required, and thus this retroactive requirement may force them to lose otherwise legal food and feed products.

Due to recent supply chain disruptions, many growers are finding themselves unable to ship harvested soybeans, which they are having to store in grain bins until shipments can be arranged in the months to come. Many of these shipments will likely go to market after the rule fully takes effect. If shipments occur after February 2022, residues are detected, and retroactively-required channels of trade documents are not available, growers could have significant volumes of produce seized by the Food and Drug Administration (FDA). A reasonably average-sized grain bin 36 feet in diameter and 18 feet high can hold approximately 58,600 bushels of soybeans.[5] At the current market rate of approximately $12.20/bushel, if these soybeans were found to be adulterated due to residue presence, an individual grower could suffer nearly $715,000 in losses. Apply this experience to potentially hundreds or thousands of growers across the supply chain, and U.S. producers could be facing tens to hundreds of millions of dollars in losses of safe and otherwise legal food product, all because they fail to possess retroactively-required documents they could have had no way of knowing they would need at the time of application.

In summary, the soybean grower community stands to suffer immense, irreparable harm should this rule take effect. We object to the rule on these grounds, and request that EPA stay the rule's implementation to prevent these harms from occurring until the Agency can fully review and formally respond to objections.

Due Process Concerns

We are also greatly concerned growers and other stakeholders may have been denied sufficient opportunity to comment and object to this rule and on continued agricultural uses of chlorpyrifos. On October 12, 2021 – nearly six weeks after the rule had been published, and approximately three-quarters of the way through the legally required 60-day objection period – ASA staff discovered this docket on the Federal eRulemaking Portal was not open to accept comments. We immediately notified EPA of this finding, but it is unclear how long the Portal had not been open. The rule is very clear that objectors must file with both the Federal eRulemaking Portal and with EPA's Office of Administrative Law Judges (OALJ) e-filing system, but individuals seeking to object may not have had that opportunity.

The months of September and October, which was the window for filing objections to this rule, happen to be the primary harvest season and one of the busiest times of the year for U.S. soybean growers. If individual growers spared some of their very limited time to go online to the eRulemaking Portal and found the comment function disabled, they may not have had another opportunity to log on during this demanding season. If the Portal truly was disabled for several weeks, it is entirely possible numerous individuals would have been denied their legal right to object to this rule.

Moreover, ASA is concerned agricultural stakeholders will not have an opportunity to advocate for continued agricultural uses of chlorpyrifos during the registration review process. By issuing a final rule

[5] Dorn, Tom. University of Nebraska-Lincoln. March 26, 2012. "How to Estimate Bushels in a Round Grain Bin." *CropWatch.* https://cropwatch.unl.edu/how-estimate-bushels-round-grain-bin

to revoke tolerances and the Agency indicating that it will not further consider agricultural uses as part of the ongoing registration review process,[6] stakeholders have no mechanism to contend for continued agricultural uses. Behind closed doors without public input, EPA unilaterally and inappropriately decided to revoke all tolerances and has indicated it will cancel all agricultural uses. This is not how Congress intended the standard notice and comment process to occur when it enacted the Administrative Procedure Act. We object to the rule on the basis that we do not believe EPA has followed legal due process requirements to allow stakeholders sufficient time to object to this rule or advocate for continued agricultural uses of this pesticide.

Finding that Soybean Uses Pose Dietary Risk – Request for Evidentiary Hearing

We further object to this rule based on EPA's errant finding that the Agency cannot with reasonable certainty be confident that chlorpyrifos residues resulting from soybean uses do not pose an aggregate dietary risk warranting revocation. Pursuant to 40 CFR 178.27, we request EPA grant an evidentiary hearing to review this factual matter.

Through this rule, EPA is revoking all tolerances, including those for soybeans, citing as its justification for this action that the Agency "cannot determine that there is a reasonable certainty that no harm will result from aggregate exposure to residues, including all anticipated dietary (food and drinking water) exposures and all other exposures for which there is reliable information." Further, EPA has indicated it will formally cancel these uses in a separate rulemaking in the near future.[7] We contend this underlying finding that soybean uses of chlorpyrifos might pose a potential dietary risk of concern – the very claim prompting the revocation action of this tolerance – is a factually inaccurate determination by EPA.

As part of its ongoing registration review process, EPA published a proposed interim decision (PID) for the re-registration of chlorpyrifos in December 2020. Under one scenario in the PID, EPA used a heightened 10X Food Quality Protection Act (FQPA) safety standard to ascertain uses that were reasonably certain not to result in harm under a new registration. In that scenario, EPA identified 11 high-benefit crop uses of chlorpyrifos, including soybeans, that "the agency has determined will not pose potential risks of concern with a Food Quality Protection Act (FQPA) safety factor of 10X and may be considered for retention."[8] The Agency considered both food residue and drinking water risks in making this determination. As demonstrated, EPA's own career scientists have established elsewhere in its administrative record that they are reasonably certain soybean uses will not pose harm from aggregate dietary exposures. EPA's determination in this rule that soybean uses might pose an aggregate dietary risk and warrant revocation is factually inaccurate based on the Agency's own recent registration review determinations.

As ASA and others contend in our coalition objection letter dated October 19, 2021, the Court allowed EPA to retain uses of chlorpyrifos it was reasonably certain would not pose harm from aggregate dietary exposure. EPA also clearly has the legal authority to take that very action. ASA seeks an evidentiary hearing to dispute this underlying factual inaccuracy, from which our preferred remedy would be to rescind this rule in its entirety, or at a minimum have the rule modified to preserve soybean chlorpyrifos tolerances. Pursuant to 40 CFR 178.27(c), we will not be including a copy of EPA's December 2020 PID on chlorpyrifos, as we believe this document is an EPA document that is routinely available to any member of the public.

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[6] United States Environmental Protection Agency. Last Updated September 20, 2021. *Frequent Questions about the Chlorpyrifos 2021 Final Rule*. Accessed October 28, 2021. https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule

[7] Ibid.

[8] United States Environmental Protection Agency. December 3, 2020. *Chlorpyrifos Proposed Interim Registration Review Decision Case Number 0100*. 40.

Conclusion

While we have previously filed objections with other agricultural stakeholder groups citing some concerns, the irreparable harms that this rule uniquely pose to soybean producers and our ability to be good environmental stewards compels us to file these supplemental objections. Also, because we believe significant factual errors contributed to determinations in this rulemaking that will result in harm to soybean growers, we request an evidentiary hearing to dispute these matters. We are also concerned that other growers and stakeholders, who may have their own objections with this rule, have not been given sufficient opportunity to state their objections or appeal for continued agricultural uses of chlorpyrifos. These are rights guaranteed by federal statutes. Until EPA can review and formally respond to these objections, including the underlying factual concerns ASA has raised for which we request an evidentiary hearing, we urge the Agency to stay this rule to prevent from occurring the significant, irreparable harms that it otherwise will inflict on U.S. soybean producers.

Sincerely yours,

Kevin Scott
President

Gharda Chemicals International, Inc.

November 19, 2021

Via Email

Elissa Reaves
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001
Tel: 703-347-0206
Email: OPPChlorpyrifosInquiries@epa.gov
reaves.elissa@epa.gov

Re: State Registration Actions Following EPA's Final Rule Revoking All Tolerances for Chlorpyrifos (FFDCA-HQ-2021-0001; EPA-HQ-OPP-2021-0523)

Dear Dr. Reaves:

On behalf of Gharda Chemicals, Inc. ("Gharda"), I write in follow up to Gharda's objections to the U.S. Environmental Protection Agency's ("EPA" or "Agency") August 30, 2021, final rule revoking all tolerances for the pesticide chlorpyrifos (the "Final Rule") and petition to stay the effective date of the Final Rule and February 28, 2022, expiration of tolerances. I write to provide new information to EPA that Gharda has obtained since submitting its objections and stay request that is relevant to Gharda's objections and stay request, specifically Gharda's claim that it has and will continue to suffer irreparable harm as a result of EPA's Final Rule.

Gharda is in the process of renewing its state registrations for chlorpyrifos. Because of the Final Rule, the Minnesota Department of Agriculture has refused to renew Gharda's state registration for chlorpyrifos products used on food or feed for 2022. *See* Exhibit A. As a result, Gharda will be unable to distribute or sell its chlorpyrifos products registered for use on food/feed in Minnesota from January 1, 2022, through February 28, 2022—even though chlorpyrifos tolerances will remain lawfully in place during this time period under EPA's Final Rule. Gharda has heard that other states may take similar actions.

This action by the Minnesota Department of Agriculture (and potentially similar actions by other states) will further curtail the already impossibly short time period for the Final Rule's implementation and impede the ability of Gharda and others in the agricultural supply chain to exhaust existing stores of chlorpyrifos product before the tolerance expiration takes effect under the Final Rule. It is yet another harmful by-product of the already extremely damaging and legally and scientifically unsupported Final Rule.

For reasons outlined in Gharda's objections and stay request and given this new development, which exacerbates the harm to Gharda and other stakeholders as a result of the Final Rule, Gharda respectfully urges EPA to stay the effective date of the Final Rule and tolerance expiration date immediately. At a minimum, this development is another reason why EPA must decide the stay request and respond to the objections as soon as possible (and before the end of this year), so that Gharda and others can obtain a full and fair resolution of the significant issues raised in the objections to the Final Rule.

Respectfully submitted,

Ram Seethapathi
President, Gharda Chemicals International, Inc.

Cc: Ed Messina
Dana Friedman

EXHIBIT A

[redacted]

From: Rose, Paula (MDA) <paula.rose@state.mn.us>
Date: Wednesday, October 27, 2021 at 10:28 PM
To: Ram Seethapathi <sramanathan@gharda.com>
Subject: GHARDA CHEMICALS LTD_2022 MN PESTICIDE PRODUCT RENEWAL.pdf

IMPORTANT INFORMATION REGARDING ONE OR MORE OF YOUR RENEWAL PRODUCTS CONTAINING CHLORPYRIFOS

Following EPA's publication of a final rule regarding the revocation of tolerances for the active ingredient chlorpyrifos, the MDA will not be renewing chlorpyrifos products containing only food and/or feed use for 2022 as allowed by MINN. STAT. § 18B.26 Subd. 5(b).

If you wish to carry forward with the registration of your non-food and feed chlorpyrifos products with the same EPA reg. no., please provide a revised label with non-food uses only.

Your chlorpyrifos product(s) have been crossed off with a red line on your renwal.

Attached please find the most recent version of your *Minnesota Pesticide Registration Listing of 2021 Products to be Renewed for 2022*.

1. Revising Application information. If there is any incorrect information on the attached 2022 Renewal Application, cross it out and write in the correct information (e.g. change of address, new Contact/Agent person, new phone number or company name change). If you are requesting a company name change, provide documentation indicating the State(s) wherein the new company is registered as a legal entity.

2. Kelly Registration. If you are submitting renewal(s) via Kelly Registration Systems and you have a change of address, telephone number, company name change, etc. for either the Registrant or the Contact/Agent person please send this information via email to paula.rose@state.mn.us.

3. New product registrations. New product registrations must be completed and mailed separately from the Renewal process. If you are registering new pesticide products you will need to submit the items listed at https://www.mda.state.mn.us/pesticide-fertilizer/section-3-pesticide-registration, separate from the Renewal

Application.

4. Due date. Your completed Renewal Application must be **postmarked by December 31, 2021** or a late fee of $175.00 per product will be assessed.

5. Reminder. Do not submit duplicate copies of the Renewal Application or duplicate payments.

6. Minnesota Pesticide Revised Label & SDS Submission Checklists. Each time the label or safety data sheet (SDS) is changed the registrant must submit a completed Revised Pesticide Label/SDS Submission Checklist along with a digital copy of the updated label/sds. For checklist, visit Maintaining a Product Registration https://www.mda.state.mn.us/pesticide-fertilizer/section-3-pesticides.

   *Hemp Products – if your product has been recently recognized by EPA for use on hemp please be sure to submit this checklist.

7. Frequently Asked Questions. Most of the questions we receive about pesticide registration in Minnesota have been addressed on our website. Visit www.mda.state.mn.us/pesticideregistration.

Please feel free to contact me If you have any questions.

Paula Rose
State Program Administrator
Minnesota Pesticide Registration & Fertilizer Management
625 Robert Street N.
Saint Paul, MN 55155
Email: paula.rose@state.mn.us
Direct: 651.201.6583

https://www.mda.state.mn.us/

DEPARTMENT OF AGRICULTURE

DEPARTMENT OF AGRICULTURE
625 ROBERT STREET NORTH, SAINT PAUL, MN 55155-2538
WWW.MDA.STATE.MN.US

Pesticide & Fertilizer Management Division, Ph. 651-201-6583

Minn. Stat. Sec. 18B.26, Subd. 1

MINNESOTA PESTICIDE REGISTRATION LISTING OF 2021 PRODUCTS TO BE RENEWED FOR 2022

MN License #: 20057316

AGENT:

GHARDA CHEMICALS LTD
ATTN RAM SEETHAPATHI
760 NEWTOWN YARDLEY RD STE 110
NEWTOWN PA 18940

TELEPHONE: (215) 968-9474
EMERGENCY PHONE: (215) 791-0956
FAX: (215) 968-9574
E-MAIL ADDRESS: SRAMANATHAN@GHARDA.COM

REGISTRANT:

GHARDA CHEMICALS LTD
760 NEWTOWN YARDLEY RD STE 110
NEWTOWN PA 18940

For pesticide registration frequently asked questions (FAQs) see: www.mda.state.mn.us/pesticideregistration

WARNING: Unregistered products found in the channels of trade are subject to judicial or administrative action including the issuance of stop-sale/stop-use orders.

Renewal Fee Schedule	# of Products	Amount	Amount Due	
Pesticide Product Renewal (Enter Total Number of All Products)		X $350	$	600329(3100)
AG Product Waste Pesticide Program Surcharge (Enter Total Number of All Ag Products)		X $50	$	600329(3390)
NON AG Product Waste Pesticide Program Surcharge (Enter Total Number of All Non Ag Products)		X $125	$	600329(3391)
Late Fees - Product renewals postmarked after December 31st		X $175	$	600329(3500)
$400 per Ag product ($350 registration fee + $50 waste pesticide program surcharge.)				
$475 per Non Ag product ($350 registration fee + $125 waste pesticide program surcharge.)				
			TOTAL : $	

Return this form with your check made payable to:
MINNESOTA DEPARTMENT OF AGRICULTURE
Attn: Cashier
625 Robert Street North
Saint Paul, MN 55155-2538
Fees are not refundable.

NOTE: Total amount of sales of non-agricultural pesticides to be reported 60 days after the end of the calendar year (Due March 1, 2022 for sales made from January 1, 2021 through December 31, 2021). SEPARATE SALES REPORT FORMS WILL BE MAILED TO YOU AT A LATER DATE.

I hereby certify that the information contained in and submitted with this form is true and correct.

Signature: _____ Date: _____

Name (Please print): RAM SEETHAPATHI Title: _____

Contact Telephone: (215) 968-9474 Fax Number: (215) 968-9574

E-mail Address: SRAMANATHAN@GHARDA.COM

For Office Use Only

MN License #: 20057316

Legend:

R - Restricted Use

Status (1 = Discontinued 1st Year, 2 = Discontinued 2nd year, C = Cancelled)

Type - A = Animal Care; C = Crop Chemicals; D = Disinfectants and Sanitizers; F = Formulating; G = Garden and Lawn Care; H = Homeowner; I = Industrial, Rights-of-Way and Forestry; M = Miscellaneous; P = Pool, Spa, and Hot Tub; S = Structural; T = Turf and Ornamental; V = Vertebrate Control; W = Wood Preservatives

AG = Agricultural pesticide

NON AG = Non-agricultural pesticide

MINNESOTA PESTICIDE REGISTRATION LISTING OF 2021 PRODUCTS TO BE RENEWED FOR 2022

MN License #: 20057316

Item No.	EPA Reg. No.	R	Status	Complete Brand Name of Pesticide	Type	AG	NON AG	Product No. State of MN Use Only
1	93182-10			ORACLE DICAMBA AGRICULTURAL HERBICIDE	C	1		18-148030
2	93182-23			NAVIGATOR SC TERMITICIDE/INSECTICIDE	S		1	18-148029
3	93182-24			ORACLE ADVANCED HERBICIDE	C	1		20-155857
4	93182-27			GHARDA DIURON 4L HERBICIDE	C	1		20-171653
~~5~~	~~93182-7~~	~~YES~~		~~PILOT 4E CHLORPYRIFOS AGRICULTURAL INSECTICIDE~~	~~C~~	~~1~~		~~18-148027~~
~~6~~	~~93182-8~~			~~PILOT 15G CHLORPYRIFOS AGRICULTURAL INSECTICIDE~~	~~C~~	~~1~~		~~18-148028~~
				Grand Totals :				

Gharda Chemicals International, Inc.

December 13, 2021

Via Email

Elissa Reaves
Pesticide Re-Evaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001
Tel: 703-347-0206
Email: OPPChlorpyrifosInquiries@epa.gov
reaves.elissa@epa.gov

Re: Additional State Registration Actions Following EPA's Final Rule Revoking Chlorpyrifos Tolerances, and EPA's Inconsistent Action Taken With Respect to Spirodiclofen (FFDCA-HQ-2021-0001; EPA-HQ-OPP-2021-0523)

Dear Dr. Reaves:

On behalf of Gharda Chemicals International, Inc. ("Gharda"), I write again in follow up to Gharda's objections to the U.S. Environmental Protection Agency's ("EPA" or "Agency") August 30, 2021, final rule revoking all tolerances for the pesticide chlorpyrifos (the "Final Rule") and petition to stay the effective date of the Final Rule and February 28, 2022, expiration of tolerances.

First, I write to supplement Gharda's prior letter of November 19, 2021, to alert EPA that Wisconsin has now joined Minnesota in taking adverse action against Gharda's chlorpyrifos registrations for 2022, as a result of the Final Rule. The Wisconsin Department of Agriculture has notified Gharda of its intent to move Gharda's chlorpyrifos registrations to "Discontinued status" for 2022, which would prevent any distribution or sale of Gharda's chlorpyrifos products in Wisconsin as of December 31, 2021, even though the tolerances do not expire until February 28, 2022. *See* Exhibit A. As with the action by Minnesota, this action by Wisconsin would further constrict the already practically nonexistent phase-out period under the Final Rule, compounding the irreparable harm to Gharda and others in the agricultural supply chain caused by the Final Rule.

Second, it has come to Gharda's attention that, on November 19, 2021, EPA issued a notice extending the effective date of the cancellation of two registrations for spirodiclofen from December 31, 2021 to June 30, 2022, in order to further consider the registrant's request to rescind a cancellation order. EPA's rationale for doing so is that the Agency recently completed

ecological and human health risk assessments of spirodiclofen that identified risks of concern and that "[c]hanges to the spirodiclofen labels are necessary to adequately mitigate those risks." 86 Fed. Reg. 64,929, 64,930 (Nov. 19, 2021). Exhibit B. EPA's action with respect to spirodiclofen is directly at odds with the rationale the Agency used to support its Final Rule. In the Final Rule, EPA concluded that it was permitted to assess risks based only on the "currently registered uses" of chlorpyrifos and that it was thus unable to impose labeling changes and other mitigation to address drinking water concerns identified in the Agency's December 2020 Proposed Interim Decision for chlorpyrifos. This inconsistent action by EPA further underscores the arbitrary and capricious nature of the Final Rule.

In light of these developments, Gharda reiterates its plea that EPA issue a stay of the effective date of the Final Rule and tolerance expiration date immediately, at least as to the eleven high-benefit crops identified in the Agency's Proposed Interim Decision. At a minimum, Gharda requests that EPA decide the stay request and respond to the objections as soon as possible (and before the end of this year), so that Gharda and others can obtain a full and fair resolution of the significant issues raised in the objections to the Final Rule and seek relief from the irreparable harm that Gharda and others are incurring.

Respectfully submitted,

Ram Seethapathi
President, Gharda Chemicals International, Inc.

Cc: Ed Messina
Dana Friedman

EXHIBIT A

From: DATCP Pesticide Registration <datcppesticideregistration@wisconsin.gov>
Sent: Wednesday, December 8, 2021 10:4 AM
To: Csnyder <csnyder@gharda.com>
Subject: Gharda Chemicals International - Chlorpyrifos Products

To whom it may concern,

Wisconsin has received the 2022 Pesticide Manufacturer and Labeler License renewal for Gharda Chemicals International, Inc. (EPA Company Number 3182, WI license number 15434). During review of the renewal application, it was noted that two pesticide products containing the active ingredient Chlorpyrifos and labeled for use on commodities were left in Active registration status in Wisconsin for 2022. These products are as follows:

- Pilot 4E EPA Reg. No. 3182-7
- Pilot 15G EPA Reg. No. 3182-8

As you are likely aware, EPA has revoked all tolerances for Chlorpyrifos on commodities effective February 28, 2022. Products containing the active ingredient Chlorpyrifos that are labeled for use on commodities will be considered misbranded if sold after that date. Wisconsin is reaching out to registrants that have maintained Active status for their Chlorpyrifos products labeled for use on commodities in the state of Wisconsin for 2022 to inform them that while the product registrations can be maintained as Active for 2022, the affected products will not be legal for sale and may not be used on commodities after February 28, 2022. Further, any Chlorpyrifos products still Active in the state for 2022 would need to be placed into Discontinued status in a future year (preferably 2023), with all applicable discontinuation fees due ($500 per product), despite EPA s revocation of these tolerances during 2022. Wisconsin does not have a policy to allow for cancellation of these products following an EPA action.

We would like to assess Gharda Chemicals International, Inc. s rationale for keeping the above listed products in Active registration status for 2022. At this time, Wisconsin recommends that the products listed above are moved to Discontinued status for 2022 to avoid any sale or use conflicts that may occur due to EPA s revocation of tolerances for these products. Placing the products in Discontinued status for 2022 would prevent any further distribution or sales of the above products into the state as of December 31, 2021.

indly,

Monica Sipes
Regulatory Specialist Pesticide Product Registrar
Agrichemical Management Bureau - Agricultural Resource Management Division
Wisconsin Department of Agriculture, Trade and Consumer Protection
Office: (608) 22 - 536 Cell: (608) 2 -055
Email: DATCPPesticideRegistration Wisconsin.gov

Please complete this brief survey to help us improve. Thank you for your feedback

EXHIBIT B

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–277–000.

Applicants: Gulfstream Natural Gas System, L.L.C.

Description: Compliance filing: Gulfstream Order 587–Z (Docket RM96–1–042) Compliance Filing to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5067.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–278–000.

Applicants: Gulf South Pipeline Company, LLC.

Description: Compliance filing: NAESB Order 587–Z Compliance Filing to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5069.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–279–000.

Applicants: Texas Gas Transmission, LLC.

Description: Compliance filing: NAESB Order 587–Z Compliance Filing to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5070.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–280–000.

Applicants: Boardwalk Storage Company, LLC.

Description: Compliance filing: NAESB Order 587–Z Compliance Filing to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5071.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–281–000.

Applicants: High Island Offshore System, L.L.C.

Description: Compliance filing: NAESB v. 5.0 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5078.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–282–000.

Applicants: MIGC LLC.

Description: Compliance filing: NAESB V3.2 (Order No. 587–Z) Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5089.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–283–000.

Applicants: Iroquois Gas Transmission System, L.P.

Description: Compliance filing: 11.12.21 FERC Order 587–Z (NAESB) v3.2 Compliance Filing to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5095.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–284–000.

Applicants: DBM Pipeline, LLC.

Description: Compliance filing: Order No. 587–Z Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5098.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–285–000.

Applicants: ETC Tiger Pipeline, LLC.

Description: Compliance filing: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5099.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–286–000.

Applicants: Fayetteville Express Pipeline LLC.

Description: Compliance filing: Fayetteville Express Pipeline LLC submits tariff filing per 154.203: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5103.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–287–000.

Applicants: Transwestern Pipeline Company, LLC.

Description: Compliance filing: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5107.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–288–000.

Applicants: Southwest Gas Storage Company.

Description: Compliance filing: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5108.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–289–000.

Applicants: Gulf States Transmission LLC.

Description: Compliance filing: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5110.

Comment Date: 5 p.m. ET 11/24/21.

Docket Numbers: RP22–290–000.

Applicants: Florida Gas Transmission Company, LLC.

Description: Compliance filing: NAESB 3.2 Compliance to be effective 6/1/2022.

Filed Date: 11/12/21.

Accession Number: 20211112–5114.

Comment Date: 5 p.m. ET 11/24/21.

Any person desiring to protest in any the above proceedings must file in accordance with Rule 211 of the Commission's Regulations (18 CFR 385.211) on or before 5:00 p.m. Eastern time on the specified comment date.

The filings are accessible in the Commission's eLibrary system (*https://elibrary.ferc.gov/idmws/search/fercgensearch.asp*) by querying the docket number.

eFiling is encouraged. More detailed information relating to filing requirements, interventions, protests, service, and qualifying facilities filings can be found at: *http://www.ferc.gov/docs-filing/efiling/filing-req.pdf.* For other information, call (866) 208–3676 (toll free). For TTY, call (202) 502–8659.

Dated: November 15, 2021.

Debbie-Anne A. Reese,

Deputy Secretary.

[FR Doc. 2021–25253 Filed 11–18–21; 8:45 am]

BILLING CODE 6717–01–P

ENVIRONMENTAL PROTECTION AGENCY

[EPA–HQ–OPP–2017–0466; FRL–9272–01–OCSPP]

Spirodiclofen; Product Cancellation Order for Certain Pesticide Registrations; Amendment

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice.

SUMMARY: EPA issued a notice in the **Federal Register** on December 21, 2020 to amend the effective date of cancellation for the two spirodiclofen registrations listed in Table 1B of the cancellation order published in the **Federal Register** on April 13, 2018. The affected registrations for that cancellation order, EPA Registration Nos. 264–830 and 264–831 were registered to Bayer CropScience. The December 21, 2020, notice in the **Federal Register** was issued to amend the cancellation order, as requested by Bayer, by amending the effective date of the cancellation and the existing stocks provision for the two spirodiclofen registrations until December 31, 2021. Subsequent to the issuance of this cancellation order, the two registrations were transferred to the Gowan Company and Gowan has requested that the cancellation order be rescinded. EPA is extending the effective date of cancellation to June 30, 2022 while considering Gowan's request. The cancellation of these two registrations would terminate the last spirodiclofen products registered for use in the United States. Any distribution, sale, or use of the products subject to this cancellation order is permitted only in accordance with the terms of this order, including any existing stocks provisions.

DATES: The **Federal Register** of December 21, 2020, announced the voluntary cancellation of two

spirodiclofen registrations (EPA Registration Nos. 264–830 and 264–831) as requested by the registrant, effective December 31, 2021. The Agency is now amending the effective date of cancellation to June 30, 2022.

FOR FURTHER INFORMATION CONTACT: Veronica Dutch, Pesticide Re-evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW, Washington, DC 20460–0001; telephone number: (202) 566–2352; email address: *dutch.veronica@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

This action is directed to the public in general and may be of interest to a wide range of stakeholders including environmental, human health, and agricultural advocates; the chemical industry; pesticide users; and members of the public interested in the sale, distribution, or use of pesticides. Since others also may be interested, the Agency has not attempted to describe all the specific entities that may be affected by this action.

B. How can I get copies of this document and other related information?

The docket for this action, identified by docket identification (ID) number EPA–HQ–OPP–2017–0466, is available at *https://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave. NW, Washington, DC 20460–0001.

Due to the public health emergency, the EPA Docket Center (EPA/DC) and Reading Room is closed to visitors with limited exceptions. The staff continues to provide remote customer service via email, phone, and webform. For the latest status information on EPA/DC services and docket access, visit *https://www.epa.gov/dockets.*

II. What action is the Agency taking?

This notice is being issued to amend the effective date for cancellation the two spirodiclofen registrations (now EPA Registration Nos. 10163–382 and 10163–383) as published in the **Federal Register** on December 21, 2020 (85 FR 83078) (FRL 10017–47). The transfer of these spirodiclofen products to Gowan became effective on March 18, 2021. Gowan committed to develop required data with the intention of maintaining these spirodiclofen registrations in a letter dated October 8, 2020. With this notice, EPA is hereby amending the effective date for cancellation of EPA Registration Nos. 10163–382 and 10163–383 to June 30, 2022. Although Gowan submitted data and waiver requests to EPA as they had committed to do, EPA recently completed draft ecological and human health risk assessments as part of registration review which identified potential cancer dietary (water and food) risks of concern, along with potential ecological risks of concern for certain taxa, including mammals and honeybees. Changes to the spirodiclofen labels are necessary to adequately mitigate those risks. EPA is extending the effective date of cancellation to further consider Gowan's request to rescind the cancellation order. Consistent with the previous cancellation order, the registrant would be prohibited from producing, selling, or distributing existing stocks of products containing spirodiclofen following the cancellation effective date. Other entities would be permitted to sell, distribute, and use stocks of spirodiclofen until stocks are exhausted. The cancellation of these two registrations would terminate the last spirodiclofen products registered for use in the United States.

Authority: 7 U.S.C. 136 *et seq.*

Dated: November 15, 2021.

Mary Reaves,

Director, Pesticide Re-Evaluation Division, Office of Pesticide Programs.

[FR Doc. 2021–25214 Filed 11–18–21; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[CERCLA–04–2021–2504; FRL–9143–01–R4]

Horton Iron and Metal Superfund Site, Wilmington, North Carolina, Proposed Settlement

AGENCY: Environmental Protection Agency (EPA).

ACTION: Notice of proposed settlement.

SUMMARY: Under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA), the United States Environmental Protection Agency is proposing to enter into a settlement with W.R. Grace & Co. Conn concerning the Horton Iron and Metal Superfund Site located in Wilmington, North Carolina. The proposed settlement addresses recovery of CERCLA costs for a cleanup that will be performed at the Site and costs incurred by EPA.

DATES: The Agency will consider public comments on the proposed settlement until December 20, 2021. The Agency will consider all comments received and may modify or withdraw its consent to the proposed settlement if comments received disclose facts or considerations which indicate that the proposed settlement is inappropriate, improper, or inadequate.

ADDRESSES: Copies of the proposed settlement are available from the Agency by contacting Ms. Paula V. Painter, Program Analyst, using the contact information provided in this notice. Comments may also be submitted by referencing the Site's name through one of the following methods:

Internet: https://www.epa.gov/aboutepa/about-epa-region-4-southeast#r4-public-notices

Email: Painter.Paula@epa.gov

FOR FURTHER INFORMATION CONTACT: Paula V. Painter at 404 562–8887.

Maurice Horsey,

Chief, Enforcement Branch, Superfund & Emergency Management Division.

[FR Doc. 2021–25245 Filed 11–18–21; 8:45 am]

BILLING CODE 6560–50–P

ENVIRONMENTAL PROTECTION AGENCY

[ER–FRL–9059–4]

Environmental Impact Statements; Notice of Availability

Responsible Agency: Office of Federal Activities, General Information 202–564–5632 or *https://www.epa.gov/nepa.*

Weekly receipt of Environmental Impact Statements (EIS)

Filed November 5, 2021 10 a.m. EST Through November 15, 2021 10 a.m. EST

Pursuant to 40 CFR 1506.9

Notice: Section 309(a) of the Clean Air Act requires that EPA make public its comments on EISs issued by other Federal agencies. EPA's comment letters on EISs are available at: *https://cdxnodengn.epa.gov/cdx-enepa-public/action/eis/search.*

EIS No. 20210173, Draft Supplement, USACE, WA, Howard A. Hanson Dam Additional Water Storage Project, Section 902 Post Authorization Change Validation Study—Fish Passage, Draft Integrated Validation Report and Supplemental Environmental Impact Statement, Comment Period Ends: 01/04/2022, Contact: Nancy Gleason 206–764–6577.

EIS No. 20210174, Final, FERC, NY, Enhancement by Compression Project, Review Period Ends: 12/20/2021, Contact: Office of External Affairs 866–208–3372.

IN THE UNITED STATES COURT OF APPEALS
FOR THE EIGHTH CIRCUIT

RED RIVER VALLEY SUGARBEET GROWERS ASSOCIATION, ET AL. Petitioners, v. MICHAEL S. REGAN, Administrator, U.S. Environmental Protection Agency, ET AL., Respondents.	No. 22-1294

Respondents' Motion to Dismiss

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INTRODUCTION

Petitioners Red River Valley Sugarbeet Growers Association, *et al*. ("Petitioners"), seek judicial review of EPA's action entitled "Final Rule for Chlorpyrifos Tolerance Revocations," 86 Fed. Reg. 48,315 (Aug. 30, 2021) (hereinafter "Final Rule"), and of EPA's failure to act to stay the Final Rule, but this Court does not have jurisdiction over the petition. EPA issued the Final Rule under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), in response to an administrative petition, 21 U.S.C. § 346a(d)(4). Actions issued by EPA under § 346a(d)(4) are not immediately reviewable. Instead, Congress required that parties seeking to challenge such regulations first exhaust administrative remedies by filing objections with the Agency under 21 U.S.C. § 346a(g). Only *after* a party has exhausted its administrative remedies under § 346a(g) *and* EPA has issued a final order under § 346a(g)(2)(C) may the party seek judicial review of the order and any regulations subject to the final order. 21 U.S.C. § 346a(h)(1) (authorizing judicial review of "any order issued under [§ 346a(g)(2)(C)] . . . or any regulation that is the subject of such an order"). EPA has not issued its final order here, so this Court lacks jurisdiction to review the Petition.

Petitioners do not dispute that EPA has not issued a final order under § 346a(g)(2)(C) concluding the objections process. Moreover, Petitioners have not identified any statutory or regulatory authority that would allow them to

circumvent the limits Congress placed on jurisdiction under § 346a(h). It would be premature for this Court to consider the merits of EPA's Final Rule (or issue a stay as requested by Petitioners) before EPA issues its decision concluding the objections process, which EPA intends to do by February 28, 2022. Thus, the Petition for Review should be dismissed.

BACKGROUND

A. Statutory and Regulatory Background

The FFDCA authorizes EPA to establish "tolerances," which are maximum levels of pesticide residue allowed in or on food. 21 U.S.C. § 346a. Without a tolerance or exemption, pesticide residues in or on food are considered unsafe. *Id.* § 346a(a)(1). EPA "may establish or leave in effect a tolerance for a pesticide only if the Administrator determines that the tolerance is safe." *Id.* § 346a(b)(2)(A)(i). Conversely, EPA must "modify or revoke a tolerance if EPA determines that the tolerance is not safe." *Id.*

In 1996, Congress amended the FFDCA to create a new safety standard for pesticide residues, requiring EPA to determine that there is a "reasonable certainty that no harm will result" from "aggregate exposure" to pesticide chemical residues, including "all anticipated dietary exposures and other exposures" for which reliable information exists, in order to establish or leave a tolerance in effect. *Id.* § 346a(b)(2)(A)(ii). In addition, EPA must assess the risk of the pesticide residues to

infants and children utilizing a presumptive tenfold margin of safety for threshold effects unless a lower margin will be safe. 21 U.S.C. § 346a(b)(2)(C).

The FFDCA sets forth a detailed and specific process for establishing, modifying or revoking tolerances. EPA may promulgate a tolerance, on its own initiative, as a regulation under § 346a(e). Congress also authorized any person to petition EPA to issue a regulation "establishing, modifying, or revoking" a tolerance. *Id.* § 346a(d)(1)(A). In response to such a petition, EPA has several options. It may issue (1) a final regulation establishing, modifying, or revoking a tolerance; (2) a proposed regulation establishing, modifying, or revoking a tolerance; or (3) a denial of the petition. *Id.* § 346a(d)(4)(A)(i).

Congress further established an administrative process to consider objections to a regulation or an order issued under § 346a(d)(4) granting or denying a petition to establish, modify, or revoke a tolerance. Under § 346a(g)(2), any person may file written objections with EPA and may also request an evidentiary hearing on those objections. *Id.* § 346a(g)(2)(A)–(B). After considering any objections and holding any hearing, if deemed necessary, EPA must issue a final decision in the form of an order with respect to the objections. *Id.* § 346a(g)(2)(C).

Importantly, Congress provided specific requirements for judicial review of agency actions. It provided for exclusive judicial review in the United States courts of appeals of certain actions under the FFDCA. *Id.* § 346a(h). Most

important here, Congress delineated specific actions that are subject to judicial review, and EPA actions under § 346a(d)(4) responding to a petition to establish, modify, or revoke a tolerance are *not* directly reviewable. *See id*. Instead, Congress required parties aggrieved by such a petition response to first file an objection petition pursuant to Section 346a(g)(2)(C), and specified, as relevant here, that it is only EPA's final order responding to such an objections petition that is subject to judicial review (along with the regulation to which that final order relates). *Id.* § 346a(h)(1). Moreover, Congress precluded judicial review under any other provision of law as to issues that are reviewable under the FFDCA. *Id*. § 346a(h)(5). Finally, a party seeking judicial review must file a petition within 60 days of publication of the final order. *Id.* § 346a(h)(1).

B. Factual Background

1. *League of United Latin American Citizens v. Regan*

In 2007, several public interest groups including League of United Latin American Citizens ("LULAC") and others petitioned EPA under § 346a(d)(1) to revoke all existing chlorpyrifos tolerances. In 2017, EPA denied the LULAC petition after public comment. Like the Petitioners here, the LULAC petitioners prematurely sought judicial review of EPA's 2017 denial in the U.S. Circuit Court of Appeals for the Ninth Circuit. A panel of the Ninth Circuit vacated the 2017 petition denial and ordered EPA to revoke all chlorpyrifos tolerances within 60

days. *League of United Latin Am. Citizens v. EPA ("LULAC")*, 899 F.3d 814 (9th Cir. 2018). However, EPA sought rehearing en banc of the Ninth Circuit's decision on the grounds that the court lacked jurisdiction to review the 2017 denial pending an order concluding the statutorily-mandated objections process. *LULAC*, 914 F.3d 1189 (9th Cir. 2019). The Ninth Circuit granted rehearing en banc effectively vacating the panel's order. *LULAC*, 914 F.3d 1189 (9th Cir. 2019); *Advisory Committee Notes*, 9th Cir. R. 35-1 to 35-3. The Ninth Circuit sitting en banc treated the petition for review as one for mandamus relief and ordered EPA to respond to the objections to its 2017 denial within 90 days, without reaching any of the other issues in the case. *LULAC*, 922 F.3d 443 (9th Cir. 2019).

In 2019, EPA issued a final decision under § 346a(g)(2)(C) denying the LULAC petitioners' objections. In response, LULAC filed a petition for review of the 2019 order. At the outset of that proceeding, the Ninth Circuit sitting en banc dismissed the challenges to the 2017 denial as moot. *LULAC v. EPA*, 940 F.3d 1126, 1127 (9th Cir. 2019). Following briefing and oral argument on the merits of petitioners' challenges to EPA's denial of the original petition and the objections petition, on April 29, 2021, a Ninth Circuit panel vacated EPA's actions and concluded that, based on the existing record, "the only reasonable conclusion the EPA could draw is that the present tolerances are not safe within the meaning of the FFDCA." *LULAC v. EPA*, 996 F.3d 673, 680–700 (9th Cir. 2021). The court

instructed EPA to publish a final response to the 2007 petition within 60 days after the issuance of the court's mandate, without notice and comment. *Id.* at 702–703. The court further ordered that EPA's response "must be a final regulation that [1] either revokes all chlorpyrifos tolerances or [2] modifies chlorpyrifos tolerances *and* makes the requisite safety findings based on aggregate exposure, including with respect to infants and children." *Id.* at 703.

2. EPA's final rule revoking all tolerances for chlorpyrifos

On August 30, 2021, consistent with the court's order in *LULAC*, 996 F.3d at 703, EPA published the Final Rule in the Federal Register, revoking all tolerances for chlorpyrifos based on EPA's conclusion that aggregate exposures to chlorpyrifos were not safe. 86 Fed. Reg. 48,315. Petitioner Gharda and others filed objections to the Final Rule pursuant to 21 U.S.C. § 346a(g)(2)(A). EPA has not yet issued a final decision on the objections, although EPA intends to issue one by February 28, 2022. *See id.* § 346a(g)(2)(C); EPA's Opp. to Pets' Mot. to Stay, Decl. of Dr. M. E. Reaves at ¶ 25.

ARGUMENT

THE COURT LACKS JURISDICTION BECAUSE EPA HAS NOT ISSUED A FINAL DECISION UNDER 21 U.S.C. § 346a(g)(2)(C).

The Court should dismiss the petition and deny Petitioners' request for a stay because it lacks jurisdiction under the relevant FFDCA judicial review

provision, 21 U.S.C. § 346a(h). In § 346a(h), Congress did not authorize immediate judicial review for regulations like the Final Rule at issue here. Instead, Congress required that parties first file objections with the agency. *See id.* § 346a(g) (setting forth the objections process). Section 346a(h)(1) provides judicial review of regulations like the Final Rule only *after* a party has exhausted its administrative remedies *and* EPA has issued a final order under § 346a(g)(2)(C) on the objections. *Id.* § 346a(h)(1). Because, as explained below, § 346a(h)(1) says in "sweeping and direct" language that no jurisdiction exists until after EPA has issued a final order on an objection, a final order under § 346a(g)(2)(C) is a jurisdictional prerequisite and cannot be waived. *Ace Prop. & Cas. Ins. Co. v. Fed. Crop Ins. Corp.*, 440 F.3d 992, 996–97 (8th Cir. 2006). Further, Petitioners cannot evade the jurisdictional prerequisite of an order under § 346a(g)(2)(C) by fashioning their claim as one for mandamus relief.

A. The jurisdictional grant in 21 U.S.C. § 346(h)(1) extends only to a regulation that is the subject of an order under § 346(g)(2)(C).

As this Court has noted, whether "a statute requiring plaintiffs to exhaust administrative remedies" is jurisdictional depends on "the intent of Congress as evinced by the language used." *Ace*, 440 F.3d at 996. Only a statutory prerequisite that is "sweeping and direct" will be considered jurisdictional. *Id.* at 997 (quoting *Weinberger v. Salfi*, 422 U.S. 749, 757 (1975)). If the language indicates either

that "there is no federal jurisdiction prior to exhaustion" or that exhaustion is "an element of the underlying claim," it is jurisdictional. *Id.* The text of § 346a(h) requires an order under § 346a(g)(2)(C) for federal jurisdiction to exist and thus sets forth a clear jurisdictional prerequisite.

Section 346a(h) provides:

> (1) Petition
>
> In a case of actual controversy as to the validity of any regulation issued under subsection (e)(1)(C), or *any order issued under subsection (f)(1)(C) or (g)(2)(C), or any regulation that is the subject of such an order, any person who will be adversely affected by such order or regulation may obtain judicial review* by filing in the United States Court of Appeals for the circuit wherein that person resides or has its principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within 60 days after publication of such order or regulation, a petition praying that the order or regulation be set aside in whole or in part.
>
> (2) Record and jurisdiction
>
> * * * Upon the filing of such a petition, the court shall have exclusive jurisdiction to affirm or set aside the order or regulation complained of in whole or in part. As to orders issued following a public evidentiary hearing, the findings of the Administrator with respect to questions of fact shall be sustained only if supported by substantial evidence when considered on the record as a whole.
>
> * * *
>
> (5) Application
>
> Any issue as to which review is or was obtainable under this subsection shall not be the subject of judicial review under any other provision of law.

Id. § 346a(h).

Section 346a(h)(1) makes clear that the only actions subject to judicial review include: (1) "any regulation issued under subsection (e)(1)(C), or (2) any order issued under subsection (f)(1)(C) or (g)(2)(C), or (3) any regulation that is the subject of such an order." *Id*. at § 346a(h)(1). *See Natural Res. Def. Council v. Johnson*, 461 F.3d 164, 172 (2d Cir. 2006) (the FFDCA "contains no single, overarching provision governing judicial review—instead subjecting discrete agency actions to specialized review provisions.") (quotations omitted). Congress carefully enumerated those actions that are subject to exclusive judicial review under § 346a(h)(1), making clear that a regulation issued under § 346a(d)(4)(i) in response to a petition, such as the Final Rule, is not included unless it is the subject of an order under § 346a(g)(2)(C). As the Supreme Court has stressed, when a statute names only specific agency actions for judicial review, "[c]ourts are required to give effect to Congress' express inclusions and exclusions, not disregard them." *Nat'l Ass'n of Mfrs. v. DOD*, 138 S. Ct. 617, 631 (2018). Thus, an order under § 346a(g)(2) concluding the objections process is required before a court may exercise jurisdiction.

Additional textual signals in § 346a(h) confirm Congress's clear intent to limit a court's jurisdiction. Section 346a(h) is entitled "Judicial Review." Subsection (h)(1) expressly identifies which orders and regulations may be the

subject of a petition for review and does not include actions under § 346a(d)(4). Additionally, subsection (h)(2), captioned "Record and jurisdiction," makes "the filing of such a petition"—*i.e.*, a petition for review of an order specifically enumerated in section 346a(h)(1)—an express condition of the Court's exercise of "exclusive jurisdiction." Lastly, § 346a(h)(5) states that "[a]ny issue as to which review is or was obtainable under this subsection shall not be the subject of judicial review under any other provision of law."

Aside from its plain text, the legislative history of the FFDCA shows that Congress's choice to exclude from judicial review regulations establishing, modifying, or revoking a tolerance *except* those that are the subject of an order under § 346a(g)(2)(C) was intentional. Prior versions of the FFDCA permitted certain actions by EPA to be subject to *either* further administrative review or judicial review. *See* 21 U.S.C. § 346a(e), (i) (1982) (revised in 1996); *see Nat'l Coal. Against the Misuse of Pesticides v. Thomas*, 809 F.2d 875, 879 (D.C. Cir. 1987) (quoting 21 U.S.C. § 346a(e) (1982 version)). In 1996, Congress amended the statute in the Food Quality Protection Act and eliminated the opportunity for judicial review without the completion of the administrative process. Food Quality Protection Act of 1996, Pub. L. No. 104–170, 110 Stat. 1489, 1525.

Analyzing the FFDCA's amended jurisdictional provision, the Second Circuit in *Johnson* recognized its carefully constructed limiting language:

> By specifically referencing Section 346a(g)(2)(C), Section 346a(h)(1) permits review of those orders issued pursuant to Section 346a(g). Section 346a(g), in turn, permits objections to orders issued pursuant to Section 346a(d)(4), which resolve petitions to establish, modify, or revoke a tolerance under Section 346a(d)(1). Thus, *if it is or was possible to obtain review under the administrative review procedures of Section 346a(g), then Section 346a(h) limits judicial review to the courts of appeals and forecloses such review prior to the exhaustion of administrative remedies*.

461 F.3d at 173 (emphasis added).

Although a Ninth Circuit panel reviewing a premature challenge to EPA's 2017 denial of the initial 2007 petition to revoke chlorpyrifos concluded that § 346a(h)'s exhaustion requirements were not jurisdictional, that decision was effectively vacated by an order granting rehearing en banc. *LULAC*, 914 F.3d 1189 (9th Cir. 2019); *Advisory Committee Notes*, 9th Cir. R. 35-1 to 35-3; *see also In re Pesticide Action Network of N. Am.*, 863 F.3d 1131, 1132-33 (9th Cir. 2017) (recognizing § 346a(h)'s exhaustion requirements). The plain text of § 346a(h) demonstrates that a final order under § 346a(g)(2)(C) is a jurisdictional prerequisite.

Because EPA has not yet issued an order under § 346a(g)(2)(C), this Court lacks subject-matter jurisdiction and the petition should be dismissed.

B. Petitioners provide no basis for this Court to ignore the express limits on jurisdiction.

Petitioners do not appear to dispute that § 346a(h)(1) limits judicial review to only those regulations that are the subject of a final order under § 346a(g)(2)(C).

See Petition for Review ("Pet.") at 30, Dkt ID # 5126162 (acknowledging that it is EPA's "final decision" under § 346a(g)(2)(C) that "an objector may challenge in court"). Indeed, by seeking mandamus relief, Petitioners tacitly admit that this Court lacks jurisdiction to review the Final Rule absent an order under § 346a(g)(2)(C) on the pending objections. Nonetheless, they argue that the Court should ignore the express limitations of § 346a(h)(1) because awaiting EPA's final order under § 346a(g)(2)(C) would "foreclose[e] judicial review" of the revocation of the tolerances, exhaustion would be futile, and petitioners would be irreparably harmed. Pet. at 30. None of Petitioners' arguments provides a basis for this Court to ignore § 346a(h)(1)'s jurisdictional prerequisite of an order under § 346a(g)(2)(C), as subject-matter jurisdiction cannot be waived. Even if the exhaustion requirement in § 346a(h)(1) is not jurisdictional, however, it is still a statutorily mandated claims-processing rule that must be enforced, if raised, as is the case here. *United States v. Houck*, 2 F.4th 1082, 1084 (8th Cir. 2021).

The requirement that a party wishing to challenge a regulation issued under § 346a(d)(4) obtain an order under § 346(g)(2)(C) is not a mere procedural step. Rather, the jurisdictional grant in § 346a(h)(1) authorizing review of a "regulation" is limited to a "regulation that is subject to such an order" under § 346a(g)(2)(C). In other words, it is only a regulation subject to an order under § 346a(g)(2)(C) that is among the "classes of [actions] . . . falling within a court's adjudicatory

authority." *Kontrick v. Ryan*, 540 U.S. 443, 455 (2004) (discussing jurisdiction). Absent an order under § 346a(g)(2)(C), the Final Rule is simply not within the FFDCA's jurisdictional grant and subject-matter jurisdiction is lacking.

As already discussed, Congress made clear in express terms that judicial review of any order or regulation issued pursuant to the FFDCA's petition process would have to await the conclusion of the administrative objections process. Therefore, Petitioners' contention that awaiting a final order concluding the objections process would "foreclose" judicial review is a non sequitur. Section 346a(h)(1) provides for judicial review of the Final Rule *after* the conclusion of the objections process, upon the issuance of an order under § 346a(g)(2)(C). And EPA intends to issue that order by the end of this month, at which point Petitioners will have an opportunity for judicial review.

Petitioners' reliance on the D.C Circuit's decision in *Clean Air Council v. Pruitt*, 862 F.3d 1, 6 (D.C. Cir. 2017), invokes another inapt comparison. *See* Pet. at 11. In that case, the D.C. Circuit held that EPA had erred by granting a stay of a final rule issued under the Clean Air Act because it concluded that EPA had exceeded the limits that Congress had placed on such stays. Here, it is Petitioners who are trying to compel the Court to issue a stay of the Final Rule in contravention of Congress's clearly expressed intent that judicial review should

await a final decision by EPA concluding the administrative process. Neither the FFDCA nor the decision in *Clean Air Council* supports Petitioners' position.[1]

Nor can Petitioners' claim that § 346a(h)'s express jurisdictional limits can be waived because requiring exhaustion would be futile. As noted, even if § 346a(h)(1)'s exhaustion requirement were not jurisdictional, it would still be a mandatory claims processing rule that should be enforced. *See Houck*, 2 F.4th at 1084–85. Even if the Court could waive the mandatory exhaustion requirement in § 346a(h)(1), an administrative remedy is futile only "if there is doubt about whether the agency could grant effective relief." *Ace*, 440 F.3d at 1000. The question is not whether the agency *will* grant relief, but whether it could grant effective relief. Petitioners do not dispute that EPA has the authority to resolve objections under the FFDCA and that a stay or modification of the Final Rule would resolve their concerns. Thus, Petitioners cannot claim futility.

Insofar as Petitioners contend that they are seeking review of EPA's failure to respond to their administrative objections and stay request, that does not provide a route around § 346a(h)(1)'s express jurisdictional prerequisite of an order under

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[1] Nor are Petitioners aided by their reference to FDA regulations that EPA looks to for evaluating stay requests under the FFDCA. *See* Pet. at 12 n.5. Under 21 C.F.R. § 10.45(d), the agency's final decision on a stay request is a final, reviewable action. EPA has not yet issued a final decision on the administrative stay request pending before it, and therefore there is no "final action" for this Court to review.

§ 346a(g)(2)(C) either. *See Degnan v. Burwell*, 765 F.3d 805, 810 (8th Cir. 2014) (denying mandamus jurisdiction where the claimants could seek relief by exhausting their administrative remedies) (citation omitted). These limits would be meaningless if a party could avoid them merely by arguing that the agency failed to act to grant administrative relief. EPA has not unreasonably delayed in responding to objections to the Final Rule, which was only issued in August 2021. Although EPA has not yet issued an order in response to the objections, it intends to do so by February 28, 2022.[2] *See* Reaves Decl. at ¶ 25.

CONCLUSION

Because a final rule under 21 U.S.C. § 346a(d)(4)(A)(i) is not within the jurisdiction of this Court to review until EPA issues a final decision under § 346a(g)(2), which it has not done, the Court must dismiss the petition. Even if § 346a(h)(1)'s exhaustion requirement is not jurisdictional, it is still a mandatory statutory requirement that should be enforced and Petitioners fail to show otherwise.

[2] EPA reserves the right to file a further response to Petitioners' request for mandamus if the Court orders a response. 8th Cir. R. 21A; Fed. R. App. P. 21.

Respectfully submitted,

/s/ *Laura Glickman*

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February 18, 2022
DJ #1-22091

CERTIFICATE OF COMPLIANCE

1. This document complies with the type-volume limit of Federal Rule of Appellate Procedure 27(d)(2) because, excluding the parts of the document exempted by Federal Rule of Appellate Procedure 32(f) this document contains 3,611 words.

2. This document complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type-style requirements of Federal Rule of Appellate Procedure 32(a)(6) because this document has been prepared in a proportionally spaced typeface using Microsoft Word 2016 in 14-point Times New Roman font.

/s/ *Laura Glickman*
LAURA GLICKMAN
Counsel for Respondents

Declaration of Stephanie H. Stephens

I, Stephanie H. Stephens, declare as follows:

1. I am currently a Principal Scientist at Exponent, Inc. (Exponent). I have worked on pesticide registration issues for consulting companies, pesticide industry, and the United States Department of Agriculture, Animal and Plant Health Inspection Service for 30 years. I am familiar with the facts set forth in this declaration and, if called as a witness, could and would testify competently to these facts under oath.

2. I am making this declaration on behalf of Petitioner Gharda Chemicals International, Inc. (Gharda) in support of Petitioners' Reply in Support of Petitioners' Motion for A Partial Stay Pending Review. I have reviewed Respondents' Opposition to Petitioners' Motion for A Partial Stay Pending Review, in which the U.S. Environmental Protection Agency (EPA) states that "Gharda is not without a remedy. . . . Gharda and the other registrants may at any time request voluntary cancellation or modification of its registrations and petition EPA to establish new tolerances." Resp. at 17. In my decades of experience

with pesticide registration issues, it is my opinion that this is not a viable remedy.

3. On behalf of Gharda, throughout 2021 and through January 2022, I attended numerous discussions between Gharda and personnel from EPA's Office of Pesticide Programs, Pesticide Re-Evaluation Division (EPA OPP PRD). Leading up to EPA's August 2021 Final Rule revoking all tolerances for chlorpyrifos (Final Rule), these discussions focused on a possible voluntary cancellation of selected chlorpyrifos uses and associated tolerances with retention of other crop uses and associated tolerances.

4. After EPA's Final Rule, PRD proposed to Gharda that Gharda could submit an application for new food use(s) and associated tolerance(s). The applicable registration package(s) would be prepared and submitted to EPA's Registration Division (RD), which is responsible for pesticides that are considered conventional chemicals, and would be subject to the fees and timing under the current fee-for-service provisions for pesticide registrations under the Pesticide Registration Improvement Extension Act of 2018 (PRIA 4).[1] I believe this is the

[1] https://www.epa.gov/pria-fees.

regulatory "remedy" EPA's brief is referring to when it states that "Gharda . . . may at any time request voluntary cancellation or modification of its registrations and petition EPA to establish new tolerances." Resp. at 17.

5. In my experience, if Gharda were to submit an application for registration of food uses and associated tolerances while existing food uses and tolerances remained on the label (*i.e.*, before EPA revoked all tolerances and cancelled all food uses), it would take approximately 16 months from the time of submission of the application until possible EPA approval. EPA's fees for retaining U.S. food uses and associated tolerances would be approximately $525,000.

6. If Gharda were to submit applications for registration of new food uses and associated tolerances after EPA revoked all tolerances and cancelled all food uses, it would take approximately 38 months from the time of submission of the applications until possible EPA approval. EPA's fees for reestablishing U.S. food uses and associated tolerances would be approximately $875,000.

7. EPA's proposed path forward, whether done in advance of the cancellation of all food uses and associated tolerances or after all

food uses and associated tolerances are canceled, is not a viable remedy because of the significant timing and associated costs.

I, Stephanie H. Stephens, declare that the forgoing statements are true and correct to the best of my knowledge.

Dated: February 21, 2022

Stephanie H. Stephens

Stephanie H. Stephens

In the United States Court of Appeals
FOR THE EIGHTH CIRCUIT

No. 22-1294

RED RIVER VALLEY SUGARBEET GROWERS ASSOCIATION, et al.,

Petitioners,

v.

MICHAEL S. REGAN, Administrator, U.S. Environmental Protection Agency, et al.,

Respondents.

On Petition for Review from the
U.S. Environmental Protection Agency

PETITIONERS' RESPONSE IN OPPOSITION TO RESPONDENTS' MOTION TO DISMISS

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INTRODUCTION

Just one business day after filing a motion to dismiss telling this Court it had not made any final decisions, the U.S. Environmental Protection Agency ("EPA") signed a 193-page order unveiling them. *See* EPA 28(j) Letter (attachment signed February 22, 2022), Doc. ID 5130160 ("EPA's Denial"). That order denied Petitioners' objections and upheld EPA's final rule revoking all chlorpyrifos tolerances for agricultural commodities. It also confirmed EPA's denial of an administrative stay of the rule.

EPA's Denial makes clear that this Court has jurisdiction, and should proceed to rule on Petitioners' pending motion to stay, for the following reasons. First, EPA's Denial moots its motion to dismiss, which rests entirely on the idea that EPA had not reached any final decision. But even if EPA's motion were not already moot, its arguments are fatally flawed. This Court has jurisdiction to stay implementation of flawed rules under the Federal Food, Drug, and Cosmetic Act ("FFDCA") in order to avoid irreparable harm, even if objections are also pending before EPA. The FFDCA does not present a jurisdictional bar to judicial review, but rather only establishes a

requirement to exhaust administrative remedies prior to seeking judicial review. Petitioners did everything required to exhaust those remedies before coming to this Court. EPA's actions made pursuit of those remedies futile. By resolving a key legal question of statutory interpretation, this Court can avert the irreparable harm that Petitioners show would befall them following implementation of the rule on February 28, 2022. These circumstances justify waiving the exhaustion requirement in the FFDCA and granting judicial review. *Ace Prop. & Cas. Ins. Co. v. Fed. Crop Ins. Corp.*, 440 F.3d 992, 1000 (8th Cir. 2006).

Plaintiffs' motion to dismiss should either be dismissed as moot or denied on the merits, and the Court should grant the relief requested in Petitioners' pending motion to stay.

BACKGROUND

The insecticide chlorpyrifos is a major crop protection tool that growers throughout the Midwest and around the country have relied upon for decades. Pet. for Review, Doc. ID 5126162 at 12 ("Petition"). On August 30, 2021, EPA issued a final rule revoking all tolerances for the pesticide chlorpyrifos. *See Final Rule for Chlorpyrifos Tolerance*

Revocations, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"), Doc. ID 5126162 at Declaration of Nash E. Long ("Long Decl.") Ex. A. Tolerances are maximum levels of pesticide residues allowed in or on food and are regulated under the Federal Food, Drug, and Cosmetic Act ("FFDCA"), as amended by the Food Quality Protection Act ("FQPA"). EPA issued the Final Rule in response to an April 29, 2021, order of the U.S. Court of Appeals for the Ninth Circuit in *League of United Latin American Citizens v. Regan*, 996 F.3d 673, 678 (9th Cir. 2021) ("*LULAC*"), instructing EPA "either to modify chlorpyrifos tolerances *and* concomitantly publish a finding that the modified tolerances are safe," "or [if it was unable to make a safety finding,] to revoke all chlorpyrifos tolerances."

Just months before the Ninth Circuit's ruling, EPA's expert scientists issued a December 2020 Proposed Interim Registration Review Decision for Chlorpyrifos ("PID"), Doc. ID 5126162 at Long Decl. Ex. B, in which they concluded that eleven crop uses (alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugarbeet, strawberry, and wheat) in specifically designated regions are safe ("EPA's Designated Safe Uses"). Petition at 13–14. The aggregate

value of these 11 crops to the U.S. economy is more than $59 billion annually.[1] EPA has acknowledged that the use of chlorpyrifos on the 11 crops at issue provides "high benefits" to agriculture. PID at 69, Long Decl. Ex. B.

Rather than modify tolerances consistent with its finding that EPA's Designated Safe Uses are safe, EPA's Final Rule revoked ***all*** tolerances for chlorpyrifos. EPA did not have any new data or scientific analyses to support this decision. Instead, EPA's Final Rule announced—without notice and comment—a new interpretation of the law that allowed EPA to claim that its safety findings did not matter. On that basis, EPA's Final Rule eliminated chlorpyrifos tolerances for all commodities effective six months from the date of publication—on February 28, 2022. 86 Fed. Reg. at 48,336, Long Decl. Ex. A.

Petitioners are a coalition of growers and grower groups who rely on chlorpyrifos to meet their crop protection needs ("Grower Petitioners") and Gharda Chemicals International, Inc. ("Gharda"), the holder of an EPA registration for chlorpyrifos. In October 2021,

[1] USDA, National Agricultural Statistics Service, www.nass.usda.gov.

Petitioners (with the exception of Petitioner National Cotton Council) timely submitted objections to the Final Rule, pursuant to Section 408(g) of the FFDCA, 21 U.S.C. § 346a(g)(2)(A). Petition at 24–25. Separately, several Petitioners sought an administrative stay of the Final Rule. *Id.* EPA did not act on the objections or stay requests for over four months. Nevertheless, EPA stated publicly that it intended to carry out the expiration of the tolerances and corresponding cancellation of food use registrations under FIFRA, despite the ongoing administrative objections process. EPA Ltr. to Am. Soybean Ass'n (Jan. 4, 2022), Doc. ID 5126162 at Long Decl. Ex. S.

Following issuance of the Final Rule, Gharda sought to renew its state registrations for chlorpyrifos. Suppl. Seethapathi Decl., Doc. ID 5126372 ¶ 5. Because of the Final Rule, some states (including Minnesota) have declined to renew Gharda's state registration for chlorpyrifos products for use on food in 2022. *Id.* ¶ 6 & Ex. C . As a result, since January 1, 2022, Gharda has been unable to distribute or sell its chlorpyrifos products registered for use on food/feed in those states. *Id.* ¶ 5.

On February 9, 2022, Petitioners filed in this Court a petition for review of (1) EPA's failure to stay the Final Rule and (2) the Final Rule itself. Petitioners raise three legal challenges to the Final Rule. Petitioners argue EPA ignored the plain text of the FFDCA and the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA") in deciding that it was required to revoke all chlorpyrifos tolerances, including the tolerances for EPA's Designated Safe Uses, and could not modify the tolerances consistent with the science and its statutory authority. Petition at 36–40. Petitioners also argue that EPA's decision was arbitrary and capricious because EPA's explanation for its decision runs counter to the evidence and because it failed to consider important aspects of the problem. *Id.*

The next day Petitioners filed a motion for a partial stay of the Final Rule with respect to EPA's Designated Safe Uses and with respect to other uses until an appropriate existing stocks order is entered. Stay Mot., Doc. ID 5126280. Petitioners argued that they are likely to succeed on their claims that the Final Rule is unlawful, that they will suffer irreparable harm absent a stay, and that the balance of the equities and public interest support a partial stay. On February 18,

2022, EPA filed its opposition to the motion for a partial stay. Stay Opp'n, Doc. ID 5129078. With that opposition, EPA filed a motion to dismiss Petitioners' petition for review. Mot. to Dismiss, 5129068. In the motion to dismiss, EPA argued this Court lacks subject matter jurisdiction because EPA had not yet acted on Petitioners' objections. *Id.* at 11–20.

Just one business day later—on February 22, 2022—EPA signed an order ("EPA's Denial") denying the pending objections and stay requests with respect to the Final Rule. EPA's 28(j) Letter. EPA's Denial has been published in the Federal Register. 87 Fed. Reg. 11,222 (Feb. 28, 2022). EPA's Denial did not question the safety of EPA's Designated Safe Uses, or suggest that the scientific conclusions in the PID concerning EPA's Designated Safe Uses were undergoing revision.

> EPA does not dispute its own scientific conclusions and findings in the 2020 PID that the Agency could support a safety determination for the very limited and specific subset of uses identified in that document [i.e., EPA's Designated Safe Uses]. …. [A]s a legal matter, EPA could not rely on those scientific findings to support leaving the tolerances in place at the time of the final rule. Ultimately, this issue comes down to whether EPA properly interpreted its obligation under the FFDCA in assessing

> aggregate exposure to chlorpyrifos, and that is ultimately a question of law and not one of fact.

Id. at 11,241. EPA's Denial upheld the Final Rule on the basis of the same novel legal interpretation announced there—that EPA could not "modify" existing tolerances by narrowing permissible uses for chlorpyrifos. *Id.* at 11,237–38. EPA's stated reason for revoking tolerances for EPA's Designated Safe Uses therefore has nothing to do with public health or safety. EPA's justification for revoking tolerances for the uses EPA found "high benefit" and safe is a novel interpretation of the FFDCA.[2]

Petitioners have filed a second petition with this Court, seeking review of EPA's Denial and its decisions to uphold the Final Rule and reject the requests to stay it. Petitioners will soon seek to consolidate the second petition with this pending one, for efficiency and judicial economy.

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[2] As an alternative justification, EPA also claimed that it could not make a safety finding for a narrowed subset of uses unless "EPA has a reasonable basis to believe" that other uses will cease. 87 Fed. Reg. at 11,246. EPA's Denial did not disclose that EPA had a written commitment from Gharda to eliminate all uses beyond the 11 that EPA considered safe. *See id.*; Declaration of Donald McLean, Doc. ID 5126372 at Exhibit A at20.

ARGUMENT

I. EPA Motion to Dismiss is Moot.

EPA's Denial rendered moot EPA's motion to dismiss. That motion rests entirely on the fiction that EPA had not reached a final decision on Petitioners' objections and Petitioners' stay requests. Mot. to Dismiss at 11–16. By unveiling that decision on February 22, 2022, EPA resolved any dispute over whether it had a final decision that this Court could review. EPA's motion to dismiss is therefore moot. *See Clifford v. Janklow*, 747 F.2d 1229, 1230 n.2 (8th Cir. 1984) (per curiam) (contention resting upon the purported absence of a decision was mooted when a decision was issued the following day).

II. EPA's Motion Fails on the Merits.

Even if EPA's motion was not made moot by EPA's Denial, that motion fails on the merits. EPA's motion should be denied, and this Court should proceed to rule upon the fully briefed and pending motion to stay.

A. This Court has jurisdiction to stay implementation of an unlawful rule and avoid irreparable harm.

Petitioners did everything they could to avoid coming to court. After EPA issued its Final Rule without notice and comment,

Petitioners promptly filed objections, asked for an evidentiary hearing, and requested an administrative stay. No other administrative remedy was available to Petitioners.[3]

Congress required that EPA act promptly on Petitioners' objections. 21 U.S.C. § 346a(g)(2)(C) (specifying action "[a]s soon as practicable"). Rather than doing so, EPA sat on the objections and requests for relief until six days before the Final Rule took effect. EPA's Denial at 1. EPA's Denial provides no explanation for this delay. Because EPA has refused to stay the imminent implementation of the Final Rule, this Court has jurisdiction to step in and halt the irreparable harm that will result. This is so for three independent reasons.

First, the APA grants this Court authority to stay rules pending its review. 5 U.S.C. § 705. EPA does not contest that this Court is the proper one to review the Final Rule. Petition at 21. As "the reviewing

[3] EPA's suggestion that Petitioner Gharda could start a multi-year process of re-registering chlorpyrifos for a narrowed list of uses represents no solution, and would not address the irreparable harm that will accrue to the Grower Petitioners commencing with the spring 2022 planting season. Pet'rs' Reply on Mot. to Stay, Doc. ID 5129157 at 17.

court," this Court "may issue all necessary and appropriate process to postpone the effective date of an agency action or to preserve status or rights pending conclusion of the review proceedings." 5 U.S.C. § 705. EPA argues, however, that no court has the ability to stay a rule issued under the FFDCA until EPA has first ruled on any pending objections. Mot. to Dismiss at 19–20. If that were true, then EPA could issue rules regarding pesticide tolerances, sit on objections while the rules go into effect and irreparable harm accrues, and the Court could do nothing to stop it.

That cannot be the case. An agency cannot "control the timing and venue of judicial review by its own procedural maneuvers." *Solar Turbines Inc. v. Seif*, 879 F.2d 1073, 1079 (3d Cir. 1989) (rejecting agency's attempt to avoid judicial review by withdrawing its order without changing its position on the merits). Nor can a government agency "end-run judicial review by sitting on its hands and allowing a . . . request to languish in a bureaucratic black hole." *Byrd v. Haas*, 17 F.4th 692, 697–98 (6th Cir. 2021). The very text of the FFDCA demonstrates that Congress intended those harmed by an EPA action on tolerances would be able to obtain judicial review before a decision

goes into effect. 21 U.S.C. § 346a(h)(1) ("any person who ***will be adversely affected*** by such order or regulation may obtain judicial review") (emphasis added).

Moreover, EPA's argument has no limiting principle. It would apply even where EPA sets tolerances so high as to create a public health risk, and proceeds to allow that rule to take effect. So long as EPA continues to consider objections to that rule, according to EPA, the Court would be powerless to act. Such absurd constructions of statutes must be avoided. *Griffin v. Oceanic Contractors, Inc.*, 458 U.S. 564, 575 (1982). Meaningful judicial review of EPA's decisions on tolerances for pesticide residue in or on foods cannot be foreclosed. *Cf. McNary v. Haitian Refugee Ctr., Inc.*, 498 U.S. 479, 484 (1991) (declining to apply exclusive administrative jurisdiction clause when doing so would mean that "meaningful judicial review of [plaintiffs'] statutory and constitutional claims would be foreclosed"); *Iowa League of Cities v. EPA*, 711 F.3d 844, 873 (8th Cir. 2013) (warning that if courts do not police the boundaries of judicial review, "[a]n agency potentially can avoid judicial review through the tyranny of small decisions.").

Second, EPA's motion focuses entirely on whether the Court can review the Final Rule if EPA has not issued an order ruling on pending objections. In doing so, EPA relies heavily on subsection (h)(1) of the FFDCA, 21 U.S.C. § 346a(h)(1). For the reasons set forth below, EPA is wrong. *Infra* at 14-19. But EPA also misses the point: the Petition first seeks judicial review of EPA's denial of an administrative stay. Petition at 25. 21 U.S.C. § 346a(h)(1), upon which EPA's motion so heavily relies, does not contain any limitation on review of an EPA decision on an administrative stay. Rather, that provision concerns only the review of certain "order[s] or regulation[s]." The "order" referred to in 21 U.S.C. § 346a(h)(1) is EPA's order on objections under § 346a(g)(2)(C), not an order on a stay request. EPA has therefore failed to identify any authority requiring dismissal of the Petition's request to review EPA's refusal to grant an administrative stay.

Third, the facts before the Court establish a final, appealable decision on EPA's denial of an administrative stay. EPA's motion does not dispute that EPA constructively denied Petitioners' stay requests through unreasonable delay, that EPA's Denial confirms EPA's refusal to grant a stay, or that this Court has jurisdiction to review the decision

not to grant a stay. In fact, EPA concedes that under applicable regulations, "the agency's final decision on a stay request is a final, reviewable action." Mot. to Dismiss, at 19 n.1. EPA's decision to deny the stay requests was made well before Petitioners filed their Petition. Petition at 17. EPA's Denial, signed on February 22, 2022, simply made that decision public.

EPA's motion to dismiss cannot divest this Court of jurisdiction to review EPA's denial of an administrative stay. And for the reasons set forth below, this Court also has jurisdiction to review the Final Rule.

B. The FFDCA sets forth a waivable administrative exhaustion requirement.

The text of the FFDCA establishes an administrative exhaustion procedure which can be waived—not a jurisdictional bar. Statutory exhaustion requirements are "presumed to be nonjurisdictional unless Congress states in clear, unequivocal terms that the judiciary is barred from hearing an action until the administrative agency has come to a decision." *Ace Prop. & Cas. Ins. Co.*, 440 F.3d at 997 (internal quotation marks omitted). This requires "'sweeping and direct'" language directed to the courts, not directions to individual claimants. *Id.* at 998–99. The FFDCA contains no such "sweeping and direct" language aimed at the

courts. Respondents' attempt to insulate the Final Rule from judicial review therefore fails.

This Court's decision in *Ace Property and Casualty Insurance Co.*, illustrates the distinction between waivable exhaustion requirements and true jurisdictional limitations. In that case, this Court considered the Federal Crop Insurance Act's ("FCIA") provision stating that "a person shall exhaust all administrative appeal procedures established by the Secretary or required by law before the person may bring an action in a court of competent jurisdiction." *Id.* at 997 (emphases, footnote, and citation omitted). This Court noted that nothing in this provision "mentions, defines or limits federal jurisdiction." *Id.* at 999 (internal quotation marks omitted). This Court therefore found such language was "nothing more than a codified requirement of administrative exhaustion and is thus not jurisdictional." *Id.* at 999 (internal quotation marks omitted). In contrast, this Court cited Section 242 of the Immigration and Nationality Act ("INA") as an example of the type of "sweeping and direct" jurisdictional provision directed to a court. *Id.* at 998. That statute provides that "'a court may review a final order of removal only if . . . the alien has exhausted all

administrative remedies available to the alien as of right.'" *Id.* (quoting 8 U.S.C. § 1252(d)(1) (alteration omitted)). The INA provision, this Court held, "explicitly limits subject matter jurisdiction" and "has consistently been treated as a jurisdictional statute and an integral part of the statute." *Id.*

The provision of the FFDCA on which EPA's motion relies, 21 U.S.C. § 346a(h)(1), does not contain the kind of "sweeping and direct language" that this Court has held establishes a jurisdictional requirement. It does not "mention[], define[] or limit[] federal jurisdiction." *Id.* at 999 (internal quotation marks omitted). Rather, the FFDCA provides for an administrative procedure to occur prior to judicial review, whereby certain orders and regulations can be reconsidered on objection from an interested party. 21 U.S.C. § 346a(g)(2) ("Further proceedings"). Including such a procedure makes sense, where the statute allows for some orders and regulations to be issued without notice and comment, *id.* § 346a(l)(3)(A), or following expedited process, *id.* § 346a(d)(4)(C).

Subsection (h)(1) then provides that "any person who will be adversely affected by such order" resolving the objections lodged under

subsection (g)(2)(C) "may obtain judicial review by filing in the United States Court of Appeals for the circuit wherein that person resides or has its principal place of business." *Id.* § 346a(h)(1). Like the FCIA at issue in *Ace Property and Casualty Insurance Co.*, this provision is directed at the litigant rather than the court. Also like the FCIA, § 346a(h)(1) sets forth the timing ("within 60 days after publication") and location for the individual to seek review. 21 U.S.C. § 346a(h)(1). The FFDCA clearly establishes an administrative exhaustion requirement, not a jurisdictional bar. The text of the FFDCA lacks the "clear, unequivocal terms" necessary to overcome the presumption that exhaustion is nonjurisdictional. *Ace Prop. & Cas. Ins. Co.*, 440 F.3d at 997. EPA has not pointed to a single case in which the FFDCA—or any similar provision—has been found to establish a jurisdictional prerequisite to judicial review.[4] In sum, 21 U.S.C. § 346a(h)(1) does not limit this Court's jurisdiction to review the Final Rule.

[4] The *LULAC* litigation cited by Respondents does not contain any such finding. Although the *en banc* court there vacated the panel opinion, it did not criticize the panel's interpretation of subsection (h)(1). Nor did it need to do so, as the petition at issue contained an alternative request for relief—mandamus.

Subsection (h)(2)'s "record and jurisdiction" provision does not change the plain meaning of Subsection (h)(1). *Id.* § 346a(h)(2). Subsection (h)(2) simply states that "[u]pon the filing of such a petition, the court shall have exclusive jurisdiction to affirm or set aside the order." Thus, ***once a petition is filed***, the court of appeals has exclusive jurisdiction over the matter. Subsection (h)(2) says nothing about whether the exhaustion of administrative remedies is a jurisdictional requirement that must be met ***before*** a petition is filed.[5]

EPA's alternative argument—that if § 346a(h)(1) is not jurisdictional, then it represents a claim-processing rule (Mot. to Dismiss at 12)—also fails. Subsection (h)(1) does not fit the definition of a claim-processing rule. Claim-processing rules "seek to promote the orderly progress of litigation by requiring that parties take certain procedural steps at certain specified times." *Manrique v. United States*, 137 S. Ct. 1266, 1272 (2017) (internal quotation marks omitted). For example, the requirement that a defendant file a timely notice of appeal

[5] The legislative history Respondents cite (Mot. to Dismiss at 10) shows only that Congress intended to include administrative exhaustion requirements, not that it intended those requirements to be jurisdictional.

from an amended judgment imposing restitution is a claim processing rule. *Id.* So too is the text of 18 U.S.C. § 3582(c)(1)(A), the statute at issue in *United States v. Houck*, 2 F.4th 1082 (8th Cir. 2021). Section 3582(c) expressly limits the jurisdiction of the federal courts: "The court may not modify a term of imprisonment once it has been imposed," subject to certain narrowly defined exceptions. One of those exceptions is provided in § 3582(c)(1)(A). That exception to the jurisdictional bar on modifying sentences explicitly requires a defendant to first exhaust all administrative remedies before going to court. *Id.* § 3582(c)(1)(A) (defendant may apply to court for relief "***after*** the defendant has ***fully exhausted*** all administrative rights") (emphases added).

The language of § 346a(h)(1) contains none of the indicia of a claim-processing rule. Neither alone, nor in combination with § 346a(g)(2)(C), does § 346a(h)(1) clearly and expressly require a person to have obtained a written denial of objections before that person can seek review of the underlying regulation. Congress expressly provided that judicial review be available before the harmful effect of a regulation arises. 21 U.S.C. § 346a(h)(1) ("any person ***who will be adversely affected*** by such order or regulation may obtain judicial

review") (emphasis added). The FFDCA can be properly understood only as requiring a litigant to pursue administrative remedies before seeking judicial review. That requirement was met here.[6]

In sum, the FFDCA's establishment of an administrative procedure for objections to a faulty rule does not bar the Court from reviewing such a rule before EPA acts on those objections. The FFDCA sets forth only an administrative procedure that can be waived in order to provide meaningful judicial review. For the reasons discussed below, ample grounds exist for waiver of any administrative exhaustion requirement.

C. This Court should waive the FFDCA's administrative exhaustion requirement.

Even where a statute codifies administrative exhaustion requirements, a party may be excused from exhausting those administrative remedies. Courts will waive administrative exhaustion requirements incorporated in federal statutes "if the complaint involves

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[6] The purpose of a claim-processing rule is "to promote the orderly progress of litigation." *Manrique*, 137 S. Ct. at 1272. It does not serve to promote the orderly progress of litigation for EPA to sit on properly filed objections or stay requests, while the Final Rule takes effect in states such as Minnesota and irreparable harm begins to accrue. *Supra* at 5.

a legitimate constitutional claim, if exhaustion would cause irreparable harm, if further administrative procedures would be futile or if the issues to be decided are primarily legal rather than factual." *Ace Prop. & Cas. Ins. Co.*, 440 F.3d at 1000 (internal citation omitted). There are at least three independent grounds here for waiver of any administrative exhaustion requirement under the FFDCA.

First, further exhaustion was and would be futile. EPA's Denial represents a final order on Petitioners' objections and stay requests. EPA's work was complete well before EPA's Denial was signed on February 22, 2022. As EPA notes, it did not resolve any factual disputes or scientific issues in EPA's Denial. *Supra* at 7. Nor did EPA's Denial change any of the scientific conclusions underlying the PID or the Final Rule concerning EPA's Designated Safe Uses. In fact, EPA's Denial upheld the Final Rule on the basis of the same novel legal interpretation announced for the first time in the Final Rule itself. *See* 87 Fed. Reg. 11,239; 86 Fed. Reg. at 48,315, Long Decl. Ex. A.

EPA's Denial confirms what Petitioners laid out in the Petition—that any further administrative proceedings would be futile. Petition at 41–43. Thus, this Court should find that exhaustion of these steps was

not required prior to filing of the petition. *Coit Independence Joint Venture v. Fed. Sav. & Loan Ins. Corp.*, 489 U.S. 561, 587 (1989) ("[a]dministrative remedies that are inadequate need not be exhausted"); *In Home Health, Inc. v. Shalala*, 272 F.3d 554, 560 (8th Cir. 2001) (exhaustion excused where "further administrative procedures would be futile").[7]

Second, even if release of EPA's Denial did not confirm beyond dispute the futility of further administrative proceedings, Petitioners have shown that they will suffer irreparable harm if the revocation goes into effect. Stay Mot. at 26–30. EPA's Denial provides additional support for the conclusion that Petitioners will suffer irreparable harm from the revocation of chlorpyrifos tolerances in the Final Rule. For example, EPA continues to believe that EPA's Designated Safe Uses provide "high benefit" to agriculture. 87 Fed. Reg. at 11,246. Moreover, EPA's Denial admits that up to 20% of Minnesota's sugarbeet acreage and up to 10% of North Dakota's sugarbeet acreage could be lost due to

[7] *Houck* does not require a different result, because the statutory provision there was a true claim-processing rule, unlike the FFDCA. *Supra* at 18–19. In any event, the holding of *Houck* was narrow: "we have no ability to make an exception ***for this type*** of futility." *Houck*, 2 F.4th at 1084 (emphasis added).

the revocation of chlorpyrifos tolerances. *Id.* at 11,266. This would cause significant and irreparable harm to the sugarbeet cooperatives and sugarbeet growers included among Petitioners. Stay Mot. at 26–30. In such circumstances, exhaustion is not required. *Ace Prop. & Cas. Ins. Co.*, 440 F.3d at 1000.

Third, the main issue before the Court is a legal question, not a factual issue or a scientific dispute. EPA's Denial confirms this point, stating that EPA disregarded its scientific findings in the PID concerning the safety of EPA's Designated Safe Uses on the basis of a legal theory. "[A]s a legal matter, EPA could not rely on those scientific findings to support leaving the tolerances in place . . . . Ultimately, this issue comes down to whether EPA properly interpreted its obligations under the FFDCA . . . ." 87 Fed. Reg. at 11,241. The Court can waive the FFDCA exhaustion requirement for this reason alone. *Ace Prop. & Cas. Ins. Co.*, 440 F.3d at 1000.[8]

[8] EPA's reliance on *In re Pesticide Action Network of North America*, 863 F.3d 1131, 1132-33 (9th Cir. 2017), is misplaced. In that case, the petitioners sought mandamus compelling EPA to act on their petition, EPA denied the petition, and the petitioners promptly filed a motion for further mandamus relief, arguing EPA's denial was inadequate. *Id.* The court rejected that motion because the mandamus proceeding concerned the timing not the substance of EPA's decision

For all the foregoing reasons, the Court should waive any FFDCA exhaustion requirement, deny Respondents' Motion to Dismiss, and proceed to rule on Petitioners' Motion to Stay.

CONCLUSION

The motion to dismiss should be dismissed as moot, or denied on the merits.

February 28, 2022

Respectfully submitted,

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and petitioners had not even filed objections yet. *Id.* Here, Petitioners timely filed objections on the Final Rule; EPA has now denied those objections. EPA's Denial.

Association, American Sugarbeet Growers Association, Southern Minnesota Beet Sugar Cooperative, American Crystal Sugar Company, Minn-Dak Farmers Cooperative, American Farm Bureau Federation, American Soybean Association, Iowa Soybean Association, Minnesota Soybean Growers Association, Missouri Soybean Association, Nebraska Soybean Association, South Dakota Soybean Association, North Dakota Soybean Growers Association, National Association of Wheat Growers, Cherry Marketing Institute, Florida Fruit and Vegetable Association, Georgia Fruit and Vegetable Growers Association, and National Cotton Council of America

CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Petitioners' Response in Opposition to Respondents' Motion to Dismiss complies with the type-volume limitation of Federal Rule of Appellate Procedure because it contains 4,711 words. This Response complies with the typeface and the type style requirements of Federal Rule of Appellate Procedure 27 because this brief has been prepared in a proportionally spaced typeface using Word 14-point Century Schoolbook typeface.

Dated: February 28, 2022

s/ Nash E. Long
Nash E. Long

CERTIFICATE OF SERVICE

I hereby certify that on February 28, 2022, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Eighth Circuit by using the CM/ECF system, which will send a notice of electronic filing to all parties on the electronic filing receipt. Parties may access this filing through the Court's system.

Dated: February 28, 2022

s/ Nash E. Long
Nash E. Long

In the United States Court of Appeals
FOR THE EIGHTH CIRCUIT

No. _____

RED RIVER VALLEY SUGARBEET GROWERS ASSOCIATION; U.S. BEET SUGAR ASSOCIATION; AMERICAN SUGARBEET GROWERS ASSOCIATION; SOUTHERN MINNESOTA BEET SUGAR COOPERATIVE; AMERICAN CRYSTAL SUGAR COMPANY; MINN-DAK FARMERS COOPERATIVE; AMERICAN FARM BUREAU FEDERATION; AMERICAN SOYBEAN ASSOCIATION; IOWA SOYBEAN ASSOCIATION; MINNESOTA SOYBEAN GROWERS ASSOCIATION; MISSOURI SOYBEAN ASSOCIATION; NEBRASKA SOYBEAN ASSOCIATION; SOUTH DAKOTA SOYBEAN ASSOCIATION; NORTH DAKOTA SOYBEAN GROWERS ASSOCIATION; NATIONAL ASSOCIATION OF WHEAT GROWERS; CHERRY MARKETING INSTITUTE; FLORIDA FRUIT AND VEGETABLE ASSOCIATION; GEORGIA FRUIT AND VEGETABLE GROWERS ASSOCIATION; NATIONAL COTTON COUNCIL OF AMERICA; AND GHARDA CHEMICALS INTERNATIONAL, INC.,

Petitioners,

v.

MICHAEL S. REGAN, ADMINISTRATOR, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AND UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondents.

On Petition for Review from the
U.S. Environmental Protection Agency

PETITION FOR REVIEW

RULE 26.1 CORPORATE DISCLOSURE STATEMENT

Pursuant to Rule 26.1 of the Federal Rules of Appellate Procedure and 8th Cir. R. 26.1.A,

1. **Red River Valley Sugarbeet Growers Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

2. **U.S. Beet Sugar Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

3. **American Sugarbeet Growers Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

4. **Southern Minnesota Beet Sugar Cooperative** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

5. **American Crystal Sugar Company** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

6. **Minn-Dak Farmers Cooperative** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

7. **American Farm Bureau Federation** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

8. **American Soybean Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

9. **Iowa Soybean Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it

does not have any stock which can be owned by a publicly held corporation.

10. **Minnesota Soybean Growers Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

11. **Missouri Soybean Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

12. **Nebraska Soybean Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

13. **South Dakota Soybean Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

14. **North Dakota Soybean Growers Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

15. **National Association of Wheat Growers** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

16. **Cherry Marketing Institute** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

17. **Florida Fruit and Vegetable Association** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

18. **Georgia Fruit and Vegetable Growers Association** states that it is a not for profit corporation, that it is not a subsidiary of

any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

19. **National Cotton Council of America** states that it is a not for profit corporation, that it is not a subsidiary of any corporation, and that it does not have any stock which can be owned by a publicly held corporation.

20. **Gharda Chemicals International Inc.** states that it is a Delaware corporation, that it is a wholly owned subsidiary of its parent corporation, Gharda Chemicals Ltd., and that no other corporation holds 10% or more of the stock of Gharda Chemicals International, Inc.

Summary of Grounds for Petition

Petitioners Red River Valley Sugarbeet Growers Association, US Beet Sugar Association, American Sugarbeet Growers Association, Southern Minnesota Beet Sugar Cooperative, American Crystal Sugar Company, Minn-Dak Farmers Cooperative, American Farm Bureau Federation, American Soybean Association, Iowa Soybean Association, Minnesota Soybean Growers Association, Missouri Soybean Association, Nebraska Soybean Association, South Dakota Soybean Association, North Dakota Soybean Growers Association, National Association of

Wheat Growers, Cherry Marketing Institute, Florida Fruit and Vegetable Association, and Georgia Fruit and Vegetable Growers Association, National Cotton Council of America and Gharda Chemicals International, Inc. hereby petition the United States Court of Appeals for the Eighth Circuit for review of (1) the U.S. Environmental Protection Agency's ("EPA") final rule entitled "Chlorpyrifos; Tolerance Revocations," issued on August 30, 2021, published at 86 Fed. Reg. 48,315 (the "Final Rule") (Att. 1, Long Decl. Ex. A); (2) EPA's constructive denial of Petitioners' requests for an administrative stay of the Final Rule; and (3) EPA's order denying Petitioners' objections to the Final Rule and confirming denial of Petitioners' requests for an administrative stay of the Final Rule, entitled "Chlorpyrifos; Final Order Denying Objections, Requests for Hearings, and Requests for a Stay of the August 2021 Tolerance Final Rule" issued on February 22, 2022 and published at 87 Fed. Reg. 11222 ("EPA's Denial") (Att. 1, Long Decl. Ex. FF). As a result of EPA's Denial, the Final Rule takes effect on today's date, February 28, 2022.

Petitioners previously filed a petition for review of EPA's Final Rule in this Court on February 9, 2022, Case No. 22-1294. Petitioners

described the irreparable harm they have and will continue to suffer as a result of the Final Rule and sought a partial stay of that rule to allow continued use of chlorpyrifos for certain limited uses that EPA found to be safe ("EPA's Designated Safe Uses"). Petitioners also sought a partial stay of the tolerance expiration date for all other crop uses of chlorpyrifos until EPA issues an appropriate existing stocks order for those uses. Petitioners' motion to stay remains pending.

Now that EPA has released an order ruling on Petitioners' objections and requests for an administrative stay, Petitioners file this second petition to confirm that they are challenging (1) the Final Rule, (2) EPA's constructive denial of their requests for an administrative stay of the Final Rule, and (3) EPA's decisions in EPA's Denial overruling their objections to the Final Rule and confirming denial of Petitioners' requests to stay the Final Rule. EPA's constructive denial of Petitioners' requests for administrative stay and rejection of Petitioners' objections and requests to stay the Final Rule are arbitrary and capricious and contrary to law, including but not limited to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 346a, and the Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. § 136 *et*

seq., for the same reasons set forth in Petitioners' petition and partial motion to stay in Case No. 22-1294.

This Court has jurisdiction to consider this petition under 21 U.S.C. § 346a(h)(1), and has authority to stay implementation of the Final Rule under 5 U.S.C. § 705.[1] A stay of the Final Rule is necessary to prevent irreparable harm, as set forth in the declarations submitted in support of this petition. *See* Att. 2, Exs. A-W and Declaration of Ram Seethapathi on Behalf of Petitioner Gharda Chemicals International, Inc.

Given the significant overlap of the issues raised by both petitions, Petitioners will soon be filing a motion to have this matter consolidated with Case No. 22-1294.

[1] In a notice filed pursuant to FRAP 28(j) in Case No. 22-1294, EPA suggested that Petitioners would have to wait 14 days after publication of EPA's Denial in the Federal Register before Petitioners could challenge it. Respondents' Rule 28(j) Notice, Doc. 5130160 at 1. That assertion is contrary to, *inter alia*, the FFDCA judicial review provision in 21 U.S.C. § 346a(h)(1). EPA cannot delay judicial review of the Final Rule, which is now in effect.

February 28, 2022

Respectfully submitted,

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Vegetable Association, and Georgia Fruit and Vegetable Growers Association, and National Cotton Council of America

CERTIFICATE OF SERVICE

I hereby certify that I have, on this day, served by certified mail, return receipt requested, a copy of the foregoing document upon the following parties:

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Dated: February 28, 2022

s/ Nash E. Long
Nash E. Long

In the United States Court of Appeals

FOR THE EIGHTH CIRCUIT

No. 22-1422

RED RIVER VALLEY SUGARBEET GROWERS ASSOCIATION; U.S. BEET SUGAR ASSOCIATION; AMERICAN SUGARBEET GROWERS ASSOCIATION; SOUTHERN MINNESOTA BEET SUGAR COOPERATIVE; AMERICAN CRYSTAL SUGAR COMPANY; MINN-DAK FARMERS COOPERATIVE; AMERICAN FARM BUREAU FEDERATION; AMERICAN SOYBEAN ASSOCIATION; IOWA SOYBEAN ASSOCIATION; MINNESOTA SOYBEAN GROWERS ASSOCIATION; MISSOURI SOYBEAN ASSOCIATION; NEBRASKA SOYBEAN ASSOCIATION; SOUTH DAKOTA SOYBEAN ASSOCIATION; NORTH DAKOTA SOYBEAN GROWERS ASSOCIATION; NATIONAL ASSOCIATION OF WHEAT GROWERS; CHERRY MARKETING INSTITUTE; FLORIDA FRUIT AND VEGETABLE ASSOCIATION; GEORGIA FRUIT AND VEGETABLE GROWERS ASSOCIATION; NATIONAL COTTON COUNCIL OF AMERICA; AND GHARDA CHEMICALS INTERNATIONAL, INC.,

Petitioners,

v.

MICHAEL S. REGAN, ADMINISTRATOR, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AND UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondents.

On Petition for Review from the
U.S. Environmental Protection Agency

DECLARATION OF RAM SEETHAPATHI IN SUPPORT OF PETITION FOR REVIEW, RENEWED MOTION FOR PARTIAL STAY, AND MOTION TO FILE CONFIDENTIAL INFORMATION UNDER SEAL

I, Ram Seethapathi, declare as follows:

1. I am the President of Petitioner Gharda Chemicals International, Inc. ("Gharda"). I am authorized to make this affidavit on behalf of Gharda and have personal knowledge of all facts set forth herein.

2. I have a degree in Agricultural Sciences with a specialization in Entomology from Tamil Nadu Agricultural University; I was a Gold Medalist there, with a 4.0 GPA. I also have a diploma in General Management from the Indian Institute of Management Ahmedabad. I have been working for over four decades in the agricultural chemical industry at various levels, first in field development with Bayer, then as Regional Sales manager for Shell, and finally for eighteen years with Dow AgroSciences LLC (now Corteva Agriscience) in the Agricultural Chemicals Division, with progressively increasing responsibilities as Commercial Manager, Business Leader, and Human Resources Leader. While at Dow AgroSciences, I was involved very closely in chlorpyrifos market expansion from the early phase of the product lifecycle, including assisting in establishing a new manufacturing site in India and providing extensive training to employees working there. I was

also the Safety Coordinator for Dow AgroSciences for the Asia Pacific region. I joined Gharda fourteen years ago, providing leadership for their business in North America.

3. I also serve as Administrative Committee Chair for two important Industry taskforces, the Outdoor Residential Exposure Taskforce (ORETF) and the Agricultural Re-entry Taskforce (ARTF). In addition, I serve on the Executive Committee for the Agriculture Handler Exposure Taskforce (AHETF). These taskforces are consortia of agrochemical companies that coordinate to jointly develop scientific studies in support of pesticide registrations.

4. On August 30, 2021, the U.S. Environmental Protection Agency ("EPA" or "Agency") issued a final rule revoking all tolerances for the insecticide chlorpyrifos. Final Rule for Chlorpyrifos Tolerance Revocations, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"). In October 2021, Gharda and others filed administrative objections to and requests to stay the Final Rule. A true and correct copy of Gharda's Objections to the Final Rule Revoking All Tolerances for Chlorpyrifos (Oct. 22, 2021) is attached as Exhibit 1. A true and correct copy of Gharda's Petition to Stay the Effective Date of the Revocation of All

Tolerances for Chlorpyrifos (Oct. 22, 2021) is attached as Exhibit 2. A true and correct copy of the Declaration of Ram Seethapathi (Oct. 21, 2021), submitted in support of Gharda's Objections to the Final Rule Revoking All Tolerances for Chlorpyrifos and Petition to Stay the Effective Date of the Revocation of All Tolerances for Chlorpyrifos ("October 2021 Seethapathi Declaration") is attached as Exhibit 3. A true and correct copy of the Declaration of Dr. Richard Reiss (Oct. 21, 2021), submitted in support of Gharda's Objections to the Final Rule Revoking All Tolerances for Chlorpyrifos and Petition to Stay the Effective Date of the Revocation of All Tolerances for Chlorpyrifos is attached as Exhibit 4. EPA denied Gharda's objections to and petition to stay the Final Rule in a decision dated February 22, 2022 and published in the Federal Register on February 28, 2022. Chlorpyrifos; Final Order Denying Objections, Requests for Hearings, and Requests for a Stay of the August 2021 Tolerance Final Rule, 87 Fed. Reg. 11,222 (Feb. 28, 2022) ("EPA's Denial"). I submit this declaration in support of Petitioners' Petition for Review, Petitioners' Renewed Motion for Partial Stay, and Gharda's Renewed Motion to File Confidential Information Under Seal.

Background on Gharda and Its Role in the Chlorpyrifos Market

5. Established in 1967, Gharda is a research-based company leading in the field of agrochemical manufacturing. Gharda was founded by Dr. Keki Hormusji Gharda, a prominent chemical engineer and chemist. After obtaining a Masters degree and Ph.D. in Chemical Engineering from the University of Michigan, Ann Arbor, Dr. Gharda established Gharda Chemicals in a small rented shed. More than four decades of innovation and investment in R&D has transformed Gharda into a successful pioneer agrochemical company. Gharda's product portfolio includes a wide range of insecticides and herbicides, including chlorpyrifos, for which it holds an EPA registration. Prior to EPA's Denial, Gharda sold end-use chlorpyrifos products under the brand name Pilot™ as well as technical grade chlorpyrifos for manufacturing use.

6. Chlorpyrifos is a vitally important agricultural tool, protecting over fifty valuable U.S. food crops from destruction due to insect pests, including alfalfa, cotton, soybeans, sugarbeets, and wheat. Crops protected by chlorpyrifos are worth over a hundred million dollars annually to the U.S. economy. *See* EPA, Revised Benefits of

Agricultural Uses of Chlorpyrifos at 5, 7, EPA-HQ-OPP-2008-0850-0969 (Nov. 18, 2020) ("Revised Benefits"). Chlorpyrifos has value to growers in protecting their crops and income, as well as value to consumers who enjoy affordable, healthy, and high quality produce throughout the year.

7. Chlorpyrifos's critical importance as an insect pest management tool is due to its broad-spectrum efficacy, favorable environmental characteristics, and affordability for growers. It is the leading active ingredient to control a broad spectrum of difficult-to-control insect pests, and for some destructive pests it is the only effective pest management tool available. *Id.* at 2.

8. Because of its broad-spectrum effectiveness, chlorpyrifos is often the first tool growers employ to control new or unknown insect pests, a long-standing problem but one that will be exacerbated by climate change. *See id.* at 12–13 (removal of "broad spectrum materials such as chlorpyrifos . . . from pest management programs can result in unexpected outbreaks of previously minor pests or even the emergence of new pests"). Chlorpyrifos is also less harmful to beneficial insect populations than other insecticides. It requires fewer applications and

avoids the use of multiple chemistries to control certain pests, reducing overall insecticide use.

9. Gharda has long supported the registration of chlorpyrifos in the United States, including through an industry task force that provided financial and other support for comments, scientific data, and other materials submitted to EPA by Dow AgroSciences, LLC, now Corteva Agriscience.[1] Gharda has invested over Redacted - CBI in the development of data and other information to support the registration of chlorpyrifos in the United States.

10. In February 2020, Corteva announced that it would end production of chlorpyrifos by 2021. At that time, chlorpyrifos continued to be a critically important agricultural tool for many growers. As a result, many distributors and farm input suppliers began looking to Gharda to meet the market demand for chlorpyrifos. In response to this increase in demand, and with knowledge of the robust and growing body of scientific data supporting the safety of chlorpyrifos, Gharda

[1] A list of many of the prior comments and submissions Gharda has supported through the task force is attached as Appendix A and incorporated herein by reference and in Gharda's Objections to the Final Rule.

significantly increased its production of chlorpyrifos. Immediately prior to the Final Rule, Gharda was the primary supplier of chlorpyrifos for agricultural use in the United States.

11. Chlorpyrifos is one of Gharda's most important products. Revenues from sales of chlorpyrifos comprise a significant portion of Gharda's overall U.S. business, which prior to the Final Rule was only expected to increase. In 2020, Gharda's annual U.S. revenues from chlorpyrifos were approximately Redacted - CBI. 2021 U.S. revenues from chlorpyrifos totaled Redacted - CBI as of August 2021, and were expected to increase to Redacted - CBI by year end but totaled only Redacted - CBI as a result of the Final Rule. In 2022 and beyond, Gharda's annual U.S. revenues from chlorpyrifos were projected (before the Final Rule) to be approximately Redacted - CBI annually.

12. Gharda's position in the U.S. agrochemical industry is unique. Unlike many other registrants and leading suppliers of crop protection tools in the United States, Gharda does not have U.S.-based manufacturing facilities, which adds an additional level of complexity to the supply chain not encountered by U.S.-based manufacturers. Gharda ships materials to the United States and then uses tolling

companies to package and label the technical and end use chlorpyrifos products for sale to U.S. distributors, creating significant employment opportunities. The pandemic has exponentially increased the costs and time required to ship Gharda's materials to the U.S. for formulating, packaging, and labeling.

13. Gharda has a significant volume of raw materials on hand at its manufacturing facility in India. Gharda also has inventory of U.S. labeled chlorpyrifos product on hand at its India facility valued at approximately Redacted - CBI. In addition, Gharda has inventories of chlorpyrifos product ready for distribution in the U.S. valued at Redacted - CBI. If Gharda is unable to formulate, sell, and distribute these products for use in the 2022 growing season and beyond, Gharda will suffer Redacted - CBI economic losses. These losses are in addition to the Redacted - CBI lost investment described above in Paragraph 9 and future annual lost sales similar to those set forth above in Paragraph 11.

14. There are also significant stores of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers, estimated to be valued at approximately Redacted - CBI. (Gharda has been

specifically informed by some of its major customers that they currently have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI.)

EPA's Regulatory Processes Concerning Chlorpyrifos

15. Gharda has a vital interest in pesticide regulatory procedures and food safety standards, and in actions taken by the EPA with respect to agricultural crop protection tools, including actions that relate to pesticide residues found in or on food and the regulation of those residues under the Federal Food, Drug, and Cosmetic Act ("FFDCA") and Food Quality Protection Act ("FQPA"), and associated pesticide registration actions under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA").

16. On December 7, 2020, as part of its Registration Review of chlorpyrifos pursuant to FIFRA, EPA published its Proposed Interim Registration Review Decision for Chlorpyrifos, EPA-HQ-OPP-2008-0850-0971 (the "PID"). *See* 85 Fed. Reg. 78,849 (Dec. 7, 2020). The PID is supported by analyses included in EPA's September 21, 2020 Third Revised Human Health Risk Assessment, EPA-HQ-OPP-2008-0850-0951 (the "2020 RHHRA"), which in turn relies on, among other

documents, a September 15, 2020 Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review, EPA-HQ-OPP-0850-0941 (the "2020 DWA"). EPA's PID and 2020 DWA reflected a fulsome, measured, scientific assessment of the human health and drinking water risks of chlorpyrifos by EPA's expert scientists with respect to the eleven high-benefit uses EPA found safe.

17. In its 2020 RHHRA and PID, EPA continued to use 10% red blood cell acetyl cholinesterase inhibition ("RBC AChE") as a regulatory endpoint or point of departure for human health risk assessments for chlorpyrifos. *See* 2020 RHHRA at 2. This long-standing conservative and health-protective endpoint is supported by decades of scientific study. EPA stated that it "remains unable to verify the reported findings" of epidemiology studies claiming links between prenatal exposure to chlorpyrifos and neurodevelopmental effects. 2020 RHHRA at 89–90.

18. EPA's PID relied on the 2020 DWA, which updated and refined the Agency's 2016 DWA. In the 2020 DWA, EPA focused on eleven uses (alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugar beet, strawberry, and wheat) that EPA determined to be

high-benefit, critical crop uses. PID at 15–17. The 2020 DWA focused on select regions of the country where estimated drinking water concentrations of chlorpyrifos are below the drinking water level of concern. *Id*. In the 2020 RHHRA and PID, EPA conducted an assessment of potential risk to human health from aggregate exposure to chlorpyrifos residues, taking into account all anticipated dietary exposures from food, drinking water, and residential sources, pursuant to FFDCA Section 408(b). EPA determined that there were *no* potential risks of concern from exposure to chlorpyrifos in food or residential uses alone. 2020 RHHRA at 12; PID at 14, 18. EPA determined that risks from drinking water exposure exceeded safe levels taking into account *all* registered uses but, relying on its 2020 DWA, EPA found that risks were *below* the drinking water level of concern benchmark anticipating use only on the eleven high-benefit crops set forth above in certain identified regions of the country. PID at 18.

19. In its 2020 RHHRA and PID, EPA presented two potential approaches for assessing potential risks: (i) application of a 10X FQPA safety factor and limiting use of chlorpyrifos to the eleven high-benefit agricultural uses in select regions of the country due to "uncertainty" in

"the science addressing neurodevelopmental effects," or (ii) application of a 1X FQPA safety factor, which would allow for the retention of all currently registered uses. Regarding the first approach, EPA was unequivocal that "the agency has determined" that limiting use to the eleven "high-benefit agricultural uses" in the select geographic regions "**will not pose potential risks of concerns with an FQPA safety factor of 10X**." PID at 40 (emphasis added). EPA committed to "consider registrant and stakeholder input on the subset of crops and regions from the public comment period" and stated that it "may conduct further analysis to determine if any other limited uses may be retained." *Id.* EPA also indicated that it may further refine its assessment based on feedback and recommendations from the September 2020 FIFRA Scientific Advisory Panel. *Id.*

20. Gharda submitted comments on the PID on February 3, 2021. EPA-HQ-OPP-2008-0850-0999. Gharda urged that the weight of the scientific evidence supported application of a 1X FQPA safety factor, including a recent Corteva drinking water study of chlorpyrifos oxon submitted to the EPA on December 4, 2020, which shows that there are no drinking water risk concerns associated with chlorpyrifos oxon (the

chlorpyrifos metabolite that exists in drinking water following chlorination). *See A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days*, MRID 51392601.

Gharda's Discussions With EPA Concerning a Potential Voluntary Cancellation of Chlorpyrifos Uses

21. In April 2021, EPA regulatory personnel reached out to existing registrants to discuss whether they would entertain an agreement to voluntarily cancel some uses of chlorpyrifos. To my knowledge, EPA engaged in these discussions with the two other registrants of chlorpyrifos, Corteva AgriScience and ADAMA, Ltd. EPA's discussions with Gharda focused initially on uses identified in the PID as the 1X uses. EPA proposed a meeting with Gharda on April 20, 2021, and requested that Gharda confirm in writing in advance of that meeting Gharda's commitment to voluntarily cancel the 1X uses (while retaining the eleven high benefit crop uses identified as the 10X uses). In response, even though Gharda was confident that all 1X uses are well supported, Gharda indicated that it would consider phasing out some 1X uses on a reasonable timetable and adopting potential geographic restrictions on crop uses and other risk mitigation measures.

See October 2021 Seethapathi Decl. Ex. A. Gharda expressed concern with the Agency's proposed rushed timetable, however, given the impact of a phase-out on its business and on the grower community, and given that EPA had not yet reviewed stakeholder comments on the PID. *Id.* EPA cancelled the meeting with Gharda in order to discuss Gharda's letter further internally.

22. On April 29, 2021, the Ninth Circuit issued a decision in the lawsuit *League of United Latin American Citizens v. Regan*, consolidated Case Nos. 19-71979, 19-71982 ("*LULAC*"), which concerned EPA's handling of an administrative petition to revoke all tolerances filed by several nongovernmental organizations. In a 2-1 decision, a three-judge panel of the Ninth Circuit found that EPA's denial of objections to a 2017 order denying the administrative petition was at odds with the FFDCA because EPA did not make an affirmative finding that chlorpyrifos tolerances were "safe" in response to the petition, outside of its normal regulatory processes. *LULAC*, 996 F.3d 673 (9th Cir. 2021). The Ninth Circuit ordered EPA "either to modify chlorpyrifos tolerances and concomitantly publish a finding that the modified tolerances are safe," "or to revoke all chlorpyrifos tolerances."

Id. at 678 (emphasis added). In making this ruling the court expressly recognized the importance of the PID. Indeed, the court stated that:

> [D]uring the pendency of this proceeding, in December 2020, the EPA issued a Proposed Interim Registration Review Decision proposing to modify certain chlorpyrifos tolerances. The EPA also convened another SAP in 2020. **If, based upon the EPA's further research the EPA can now conclude to a reasonable certainty that modified tolerances or registrations would be safe, then it may modify chlorpyrifos registrations rather than cancelling them.**

Id. at 703. (emphasis added). The court ordered EPA to "correspondingly modify or cancel related FIFRA registrations for food use in a timely fashion consistent with the requirements of 21 U.S.C. § 346a(a)(1)." *Id.* at 678.

23. After the Ninth Circuit issued its decision in *LULAC*, EPA reached back out to me to resume discussions about a potential voluntary cancellation of certain chlorpyrifos uses. EPA career supervisory personnel strongly urged Gharda to agree to voluntarily cancel the 1X uses and emphasized that the Agency had limited time to decide how to implement the court's decision. In response, Gharda expressed its disagreement with the Ninth Circuit decision and hope that EPA would seek rehearing of and/or appeal the flawed decision. *See* October 2021 Seethapathi Decl. Ex. B. Nevertheless, in an effort to

work cooperatively with EPA and believing it had little choice but to accept voluntary cancellation terms, Gharda committed to voluntarily cancel yet additional 1X crop uses, pursuant to scheduled phase-outs and with appropriate existing stocks orders. *Id.* EPA strongly implied during these discussions the 10X uses would remain in place as long as Gharda voluntarily cancelled all 1X uses. *Id.* At all times during these and subsequent negotiations, Gharda understood that EPA was making decisions on a crop-by-crop/tolerance-by-tolerance basis and that EPA had the authority to modify tolerances consistent with its safety finding in the PID and interest in doing so.

24. In further discussions with EPA career supervisory personnel in late May 2021, EPA expressed to Gharda that EPA was willing to consider retention of only the 10X uses, and reiterated that it was under pressure to act quickly as a result of the Ninth Circuit decision. EPA urged Gharda to confirm in writing its agreement to voluntarily cancel all 1X uses. In response, and even though such a reduction in uses would eliminate more than 50% of Gharda's U.S. chlorpyrifos business, Gharda committed to continue working in good faith with EPA towards an agreement to voluntarily cancel all 1X uses.

See October 2021 Seethapathi Decl. Ex. C. To that end, **on June 7, 2021, Gharda confirmed in writing to EPA that it would voluntarily cancel all currently approved agricultural uses of chlorpyrifos, other than the uses identified in the PID as 10X uses**. *Id.* In turn, Gharda requested that EPA (i) work with it to address the orderly exhaustion of its inventories for the uses to be voluntarily cancelled, particularly given its unique role in the U.S. agrochemical industry; (ii) agree on orderly processes and timing for revising labels; and (iii) agree on existing stocks provisions for the uses to be voluntarily cancelled, to mitigate disruption on growers and other users. *Id.*

25. EPA career supervisory personnel were receptive to Gharda's June 7 commitment, responding the next day to ask "if Gharda is prepared to move forward with discussing voluntary use cancellations" and proposing a call with EPA legal counsel. By email dated June 8, 2021, EPA indicated that it was "considering the following dates for existing stocks:

- Technical grade active ingredient: Phase out most [1X] uses by the end of 2021; allow until the end of 2022 (12 to 18 months) for the remaining [1X] uses

- End-use products: 12 to 18 months from the technical registrants for sale/distribution of products

- End users, growers: Until exhausted"

October 2021 Seethapathi Decl. Ex. D.

26. Gharda responded to EPA's June 8 email proposing a meeting with its attorneys, with the expectation that the parties were close to reaching final agreement on terms and could begin work on modifying labels. October 2021 Seethapathi Decl. Ex. E.

27. Then, on June 14, 2021, EPA career supervisory personnel advised Gharda that Gharda's commitment regarding the "voluntary" cancellation of uses were not sufficient for EPA's "leadership," and asked Gharda to consider voluntarily cancelling yet additional uses, this time including some 10X uses, or face possible revocation of all tolerances. EPA urged Gharda to agree to voluntarily cancel all but five to six of its most important crop uses. This was the first time that EPA asked Gharda to consider voluntarily cancelling 10X crop uses. EPA also said that its leadership had raised occupational exposure concerns, and asked that Gharda agree to eliminate the use of aerial application methods, even though these are not issues to be addressed under FFDCA but are instead issues to be addressed in Registration Review

under FIFRA's risk/benefit standard. In subsequent calls, EPA also expressed concerns regarding ecological risks from chlorpyrifos, even though the ecological risk assessment for chlorpyrifos has yet to be completed. EPA nevertheless continued to indicate openness to an extended phase-out period for any voluntarily cancelled uses.

28. Gharda was confused, surprised, and disappointed at EPA's request that Gharda agree to voluntarily cancel some of the 10X uses that EPA had confirmed, in a robust scientific assessment in its PID, would not exceed safe levels. Gharda was also concerned that EPA appeared to be relying on occupational and ecological concerns as the basis for its request, neither of which relate to the regulation of tolerances under the FFDCA. Despite this dramatic and unexpected shift in the discussions, Gharda remained willing to work with EPA to try to meet its demands. Gharda repeatedly urged EPA to ensure an orderly phase-out for manufacturers, distributors, growers, and others in the agricultural supply chain for the uses to be voluntarily cancelled, as EPA's demand would eliminate nearly 80–85% of the U.S. market for chlorpyrifos.

29. Gharda and EPA had a meeting on June 24, 2021 to further discuss terms of Gharda's voluntary cancellation of registered crop uses. In a follow-up email dated June 24, 2021, approximately two months from the deadline for EPA to act in response to the Ninth Circuit order, ***EPA's Chemical Review Manager wrote Gharda*** "to confirm the uses that Gharda has agreed upon for retention following our discussions over the past few weeks and on our call this afternoon" and outlined the following terms:

- Retain alfalfa, apple, asparagus, cherry (tart), citrus, peach, soybean, sugar beet, wheat (summer and winter) in select states as outlined in the December 2020 PID
- Cotton and strawberry will be phased out over two years (until 2023)
- Aerial application will be phased out over 2 years (until 2023)
- Provisions for existing stocks:
    - Technical products [with current labels] may be sold or distributed until 12/31/2021
    - End-use products [with current labels] may be sold or distributed until 12/31/2022

See October 2021 Seethapathi Decl. Ex. F.

30. In emails dated June 25, 2021, Gharda sought clarification from EPA on some aspects of its June 25 proposal, including the details of various phase-out periods. In these emails, Gharda thanked EPA "for our good faith negotiations over the last few weeks" and said that it

"looks forward to working with the Agency to finalize the above terms." *See* October 2021 Seethapathi Decl. Ex. G. EPA proposed a meeting with its Office of General Counsel. It was Gharda's expectation that in involving legal counsel, the parties would be working to finalize a written agreement reflecting the agreed terms.

31. At EPA's request, on July 2, 2021, Gharda had a further call with EPA career supervisory personnel, during which EPA pressed Gharda to agree to voluntarily cancel even more 10X crop uses because of demands from EPA's leadership. EPA also indicated that it would not be able to agree to an extended phase out period and that chlorpyrifos applications would need to cease after six months, instead of the phase-out periods that ***EPA had proposed*** one week earlier in its June 24 email. *See supra* ¶ 29; October 2021 Seethapathi Decl. Ex. F. EPA also raised concerns with air blast applications on orchard crops. Gharda offered to provide data on mitigation measures that would address EPA's concerns regarding occupational exposure, but EPA said it would not consider mitigation data. EPA asked Gharda to put forward its best, final proposal that EPA would take back to its leadership. Gharda was especially surprised and disappointed with this

turn of events, as it in good faith believed that EPA's June 24 email, *see id.*, had set forth the final terms of crop use retention and voluntary cancellation.

32. At EPA's request, Gharda had a call with EPA and its counsel on July 6, 2021. During the call EPA pressed Gharda to accept voluntary cancellation of four 10X uses and reiterated that it would be unable to allow use of the cancelled uses beyond six months from the effective date of a final rule. EPA explained that the six-month period was based on the WTO Agreement on the Application of Sanitary and Phytosanitary measures, not because of a need for the orderly phase-out of chlorpyrifos inventories and existing stocks. Gharda explained that six months would not be a meaningful time period, given that it would largely overlap with the off season for chlorpyrifos use and because its customers purchase product at least one to two years in advance of each growing season. Following this call, Gharda followed up in writing to offer voluntary cancellation of additional 10X uses and eliminate aerial and air blast methods of application; Gharda urged EPA to extend the phase out periods for formulation, distribution, and use, to allow for an orderly exhaustion of inventories and to minimize potentially

catastrophic economic losses to Gharda and others in the supply chain, at a minimum until July 2022 to cover part of the next growing season. *See* October 2021 Seethapathi Decl. Ex. H. After this exchange, EPA indicated that it was "very close" to reaching final agreement with Gharda.

33. At EPA's request, Gharda had a further call with EPA and its counsel on July 14, 2021, during which EPA indicated that Gharda's proposal was under review by EPA leadership but that EPA hoped to have a final response within a week. EPA indicated that it would likely need a voluntary cancellation letter from Gharda quickly, to reference the voluntary cancellation in the published final rule, and would let Gharda know when to submit it. During the call, EPA, for the first time, indicated that its leadership believed that import tolerances would also need to be voluntarily cancelled. EPA could not explain the basis for this last-minute request, given that import tolerances do not raise drinking water or occupational concerns, and given that the PID did not identify any dietary (non-drinking water) risks associated with chlorpyrifos or import tolerances, even with the retention of the 10X safety factor. Nevertheless, believing it was very close to reaching final

agreement with EPA and to avoid derailing months of negotiations, Gharda submitted a proposal to EPA for the cancellation of certain import tolerances. *See* October 2021 Seethapathi Decl. Ex. I. Gharda followed up asking EPA to consider its points concerning import tolerances, but stressed that it did not want the import tolerance issue to stand in the way of resolving voluntary cancellation of uses pursuant to the terms discussed, as summarized in Gharda's July 6 email. *See* October 2021 Seethapathi Decl. Ex. J. EPA responded stating that it appreciated Gharda's engagement on this challenging issue. *See id.*

34. Following this submission and response, Gharda heard nothing further from EPA for weeks.

35. Growing increasingly concerned as the court deadline for EPA to issue a final rule was approaching, Gharda requested a meeting with EPA leadership. After Gharda's repeated outreach, EPA finally allowed Gharda to have a twenty-five-minute meeting with Assistant Administrator Michal Freedhoff and others from EPA on August 16, 2021. During the meeting, Gharda reiterated its commitment to voluntarily cancel uses as set forth above, urged EPA to make a decision consistent with science and law, and again stressed the major supply

chain disruptions and catastrophic losses that would result from a revocation of tolerances with immediate effect. EPA was silent during this meeting, indicating only that it was willing to "work collaboratively" with Gharda going forward.

36. The next day after its meeting with EPA leadership, Gharda discovered a posting on EPA's website announcing the August 2021 revocation of all tolerances for chlorpyrifos, which Gharda also discovered was posted days **before** its August 16 meeting with EPA leadership. When Gharda reached out to senior career leadership at EPA about the posting, EPA apologized for the posting and immediately removed it, but confirmed that the final rule would be consistent with the website posting. EPA indicated that there would be "elbow room" on timing of the final rule's implementation.

37. The next day, the EPA Final Rule was announced. In the Final Rule, EPA stated that it was revoking all food use tolerances for chlorpyrifos, as "[b]ased on the currently available data and taking into consideration the currently registered uses for chlorpyrifos," it was unable to make a safety finding under the FFDCA. 86 Fed. Red. 48,315. The Final Rule stated that revocations of the tolerances would

take effect on February 28, 2022, six months from the date of publication, to comply with international trade obligations. *Id*. at 48,334.

38. On August 18, 2021, the day the Final Rule was announced, EPA held a public briefing session regarding the Final Rule. EPA invited stakeholders to submit questions to EPA regarding about the Final Rule.

39. Following EPA's public briefing, Gharda and others submitted questions to EPA, concerning the Final Rule's scope, applicability, timing for implementation, and harmonization with FIFRA. Gharda specifically asked whether EPA would consider mitigation in light of Gharda's commitment to accept label modifications limiting use of chlorpyrifos to the select crop uses in select regions EPA determined in the PID were safe and what additional mitigation EPA believed it needed to act on its safety finding. Among other questions, Gharda also asked whether EPA had reviewed or was willing to consider the 2020 Corteva drinking water study.

40. On September 20, 2021, over a month after the Final Rule was announced, EPA posted responses to "Frequent Questions about

the Chlorpyrifos 2021 Final Rule" ("FAQs") on its website,[2] and responded directly to Gharda's questions that were not addressed in the FAQs. *See* October 2021 Seethapathi Decl. Ex. K. EPA's responses did not appear to allow any "elbow room" or opportunities to "work collaboratively" on the Rule's timing and implementation, but instead directed interested parties to submit objections. EPA also did not respond to Gharda's question concerning label modifications consistent with the Agency's safety finding, and indicated that "due to time constraints" it was unable "to conduct additional scientific analysis beyond what was already available at the time of the court ruling." *Id.*

41. After EPA's Final Rule, EPA proposed to Gharda that Gharda could submit an application for new food uses and associated tolerances for chlorpyrifos. Gharda's regulatory consultant advised Gharda that this process would take appropriately 16-38 months for EPA to reach a decision and cost approximately $525,000 to $875,000 in EPA fees. *See* Declaration of Stephanie Stephens, attached as Exhibit 5.

[2] https://www.epa.gov/ingredients-used-pesticide-products/frequent-questions-about-chlorpyrifos-2021-final-rule#question-2.

EPA's Inaction on Gharda's Objections and Stay Requests and Issuance of EPA's Denial

42. On October 22, 2021, Gharda submitted objections to the Final Rule, as well as a petition to administratively stay the Final Rule. *See* Exs. 1–4. EPA failed to act on the objections and stay request for over four months.

43. Faced with no other choice as the effective date of tolerance expiration was approaching, on February 9, 2022, Gharda and a coalition of growers and grower groups petitioned this Court for review of EPA's failure to stay the Final Rule and for review of the Final Rule. Case No. 22-2194, Doc. 5126162. On February 10, 2022, Petitioners filed a motion for a partial stay of the Final Rule with respect to the eleven uses EPA had found safe in the 2020 PID. EPA opposed the motion to stay and filed a motion to dismiss the Petition, claiming it had not issued a "final" decision. EPA's opposition to the motion to stay referenced two Gharda letters dated May 12, 2021 and June 7, 2021, but omitted subsequent communications. For example, EPA's opposition omitted Gharda's July 6, 2021 communication expressly setting forth Gharda's commitment to modify its registration consistent with EPA's safety finding. Case No. 22-1294, Doc. 5129078, at 16;

October 2021 Seethapathi Decl. Ex. H. In addition, EPA's opposition suggested that a voluntary cancellation agreement could not be reached because Gharda proposed terms for phased out production and exhaustion of existing stocks, when it was EPA that proposed phased out and existing stocks terms as late as June 24, 2021. *See* October 2021 Seethapathi Decl. Ex. F.

44. The next business day after it filed its motion to dismiss, EPA issued EPA's Denial, a 193-page document denying the objections to and requests to administratively stay the Final Rule in their entirety. EPA's Denial confirmed that it did not dispute any of the scientific conclusions underlying the 2020 PID or Final Rule.

45. On February 25, 2022, EPA held a meeting with registrants to review next steps in response to EPA's Denial. Gharda, Corteva, and ADAMA attended the meeting.

EPA's Denial and the Final Rule Have Caused and Will Continue to Cause Significant Harm

46. EPA's Denial and the Final Rule have caused and will continue to cause significant and irreparable harm to Gharda and others in the agricultural value chain. This is particularly so as to the six-month period for the Final Rule's implementation. When the Final

Rule was issued, the 2021 growing season had essentially ended, and chlorpyrifos will not be used until the next growing season beginning approximately in April 2022. Thus, the six month period provided in the Final Rule beginning in August 2021 and running through February 2022 is effectively meaningless and allowed no time for Gharda, distributors, and growers to phase out and exhaust existing inventories. The realities of the current supply chain were pointed out to EPA in discussions leading up to the Final Rule.

47. As a result of Gharda's increased production to meet market demand after Corteva's exit from the market, Gharda has a significant volume of raw materials and U.S. labeled product in inventory. Without the ability to formulate, distribute, and sell these products, Gharda will suffer Redacted - CBI economic losses, to say nothing of the nearly Redacted - CBI loss in its investment in chlorpyrifos and lost future sales of chlorpyrifos products in the U.S. of approximately Redacted - CBI annually. In total, the economic losses Gharda will face if tolerance revocation remains in effect will be catastrophic.

48. The harms from the Final Rule are already being felt. Because of the Final Rule, in October and December 2021, Minnesota

and Wisconsin informed Gharda that they would not renew Gharda's State registration for chlorpyrifos products for use on food or feed in 2022. As a result, since January 1, 2022, Gharda has been unable to distribute or sell chlorpyrifos products registered for use on food/feed in these key growing states—even though chlorpyrifos tolerances remained lawfully in place until February 28, 2022 under the Final Rule. I notified EPA of these actions taken by Minnesota and Wisconsin on Gharda's State registrations for chlorpyrifos, and the resulting irreparable harm to Gharda and others in the agricultural community, in correspondence to Elissa Reeves at EPA's Office of Pesticide Programs dated November 19, 2021 and December 13, 2021. True and correct copies of Gharda's November 19, 2021 and December 13, 2021 letters to EPA are attached as Exhibit 6.

49. Beyond the economic losses from the Final Rule, Gharda has suffered and will continue to suffer significant reputational harm as a result of EPA's arbitrary action against chlorpyrifos. By revoking all tolerances, EPA has directly attacked the safety of chlorpyrifos in the eyes of growers, processors, and consumers, and the credibility of Gharda in selling and distributing chlorpyrifos products. EPA has done

this despite a finding by its own expert scientists that a subset of eleven high-benefit chlorpyrifos uses in certain geographic areas are safe, and in disregard of written commitments provided to EPA by Gharda ***prior to the Final Rule*** to modify Gharda's label consistent with EPA's safety finding in its PID.

50. EPA's revocation action has and will continue to strain Gharda's relationships with its customers, who distribute its products to suppliers and end users. Indeed, during its months of negotiations with EPA, Gharda assured its customers that it was working cooperatively with EPA to reach agreement that would allow for many continued agricultural uses. Given EPA's scientific assessment in the PID which provided a clear scientific record on which to retain at least the 10X chlorpyrifos uses, neither Gharda nor its customers expected that EPA would take draconian action to eliminate all uses. EPA's abrupt departure from its own scientific findings has cast doubt on Gharda's credibility and resulted in a loss of customer goodwill.

51. In addition to the immediate and irreparable harm caused to Gharda by EPA's action, EPA's revocation action could create long-term irreparable harm to Gharda because of the stigma attached to the

unfounded public statements by EPA that its action was taken "to ensure children, farmworkers, and all people are protected from the potentially dangerous consequences of this pesticide," and "follow[s] the science and put[s] health and safety first." https://www.epa.gov/newsreleases/epa-takes-action-address-risk-chlorpyrifos-and-protect-childrens-health. There is no scientific basis for these statements, which are in fact directly at odds with EPA's Final Rule and the scientific findings set forth in the PID. *See, e.g.*, 86 Fed. Reg. at 48,324 (EPA "remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported by [epidemiology studies reporting neurodevelopmental impacts in children]"); *id.* at 48,335 ("EPA has not conducted a formal EJ analysis for this rule"); PID at 10 ("the science addressing neurodevelopmental effects remains unresolved").

52. The stigma attached to EPA's public statements not only has the potential to cause ill-will against Gharda by customers, consumers, and the public, but will also adversely affect Gharda's ability to meet the needs of growers for effective pesticide products, compounding the ill-will against Gharda. Customers who abandon Gharda products now

because of the Agency's action may not return to using products produced by Gharda even in the event of a final adjudication in Gharda's favor. Gharda may thus permanently lose a significant portion of its market share. Moreover, EPA's actions may trigger other federal or state regulatory requirements or bans, as well as restrictions by foreign governments, who look to EPA as the gold standard for making regulatory decisions based on science.

53. Losses from an immediate removal of chlorpyrifos from the U.S. market would not be borne by Gharda alone. It will also cause significant financial hardship to distributors and growers who invested substantial sums in reliance on the registration in products they are no longer able to sell or use. Most distributors purchase products from Gharda at least a year in advance, and as a result have significant product on hand in order to meet market needs and often fluctuating demand by U.S. growers. At the time of the Final Rule, Gharda had been specifically informed by some of its major customers that they have inventories of chlorpyrifos product on hand valued at approximately Redacted - CBI. Growers, for their part, not only face a lost investment in unusable product but also must find alternative,

sometimes more expensive alternative products or risk significant crop losses. In total the volume of U.S. labeled chlorpyrifos products in the hands of distributors, retailers, and growers is estimated to be valued at Redacted - CBI.

54. Commodity traders and other holders of food and feed with detectable chlorpyrifos residues face significant uncertainty, as it may be practically impossible to demonstrate that the residues result from a lawful application, particularly in the case of finished food and feed product with extended shelf lives. This confusion could result in the unnecessary waste of otherwise safe and nutritious food and feed.

55. Moreover, by insisting on giving immediate effect to the revocation actions, EPA has caused confusion on the part of the public with respect to the safety of dozens of commodities on which chlorpyrifos may legally be used.

Gharda's Confidential Business Information

56. This declaration contains confidential, competitively sensitive information on (1) the value of Gharda's investment in data and other information to support the registration of chlorpyrifos in the United States, (2) the value of U.S. labeled chlorpyrifos products held in

inventory by Gharda and its customers, and (3) Gharda's actual and projected annual revenues from sales of chlorpyrifos products in the United States. *See supra* ¶¶ 9, 11, 13–14, 47, 53. It also includes information subject to confidentiality agreements with third-parties. *See* ¶ 9. This information represents confidential financial data of Gharda, a private company, disclosure of which would cause harm to Gharda. This confidential information was submitted to EPA with Gharda's objections to and administrative petition to stay the Final Rule, under a claim of confidentiality. A true and correct copy of the October 26, 2021, cover letter to Mary Angeles transmitting Gharda's paper copies of the Business Confidentiality Asserted Objections to the Final Rule, Declaration of Ram Seethapathi, Declaration of Dr. Richard Reiss, and Petition to Stay is attached as Exhibit 7. Redactions were applied to limited portions of documents Gharda submitted to EPA's public e-rulemaking docket to protect the confidential information. EPA has not challenged Gharda's confidentiality claim as to the confidential information included in Gharda's objections to and petition to stay the Final Rule. In addition, this Court granted Gharda's motion to seal this confidential information in the earlier action Petitioners

filed challenging EPA's inaction on the objections to and requests to administratively stay the Final Rule. Case No. 22-1294, Doc. 5126372 & 5129953.

I declare that the foregoing is true and correct to the best of my knowledge.

Dated: March 3, 2022

Ram Seethapathi
President

Appendix A
List of Comments and Other Submissions to EPA Gharda has Supported Through the Chlorpyrifos Industry Task Force

1. DAS Response to 2014 Revised Human Health Risk Assessment for Chlorpyrifos, (Apr. 29, 2015), EPA-HQ-OPP-2015-0653-0214;
2. Decl. of C. Burns in support of DAS Comments on EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor Determination for Organophosphate Pesticides, (Dec. 22, 2015), EPA-HQ-OPP-2015-0653-0230 (submitted to docket EPA-HQ-OPP-2010-0119);
3. DAS Response to EPA's Proposed Rule to Revoke Chlorpyrifos Tolerances (including all references and appendices), (Jan. 4, 2016), EPA-HQ-OPP-2015-0653-0386;
4. DAS Legal and Policy Comments in Response to EPA's Proposed Rule to Revoke Tolerances for Chlorpyrifos, (Jan. 5, 2016), EPA-HQ-OPP-2015-0653-0266;
5. DAS Response to Chlorpyrifos-Methyl Human Health Draft Risk Assessment, (Sept. 15, 2015), EPA-HQ-OPP-2010-0119-0044;
6. DAS Legal and Policy Comments in Response to (i) EPA's Literature Review on Neurodevelopment Effects & FQPA Safety Factor

Determination for Organophosphate Pesticides and (ii) EPA's Chlorpyrifos-Methyl Human Health Draft Risk Assessment, (Feb. 19, 2016), EPA-HQ-OPP-2010-0119-0033;

7. DAS Comments on 2016 Revised Human Health Risk Assessment and Refined Drinking Water Assessment for Chlorpyrifos, (Jan. 17, 2017), EPA-HQ-OPP-2015-0653-0651;
8. Decl. of C. Burns in support of DAS Comments on EPA's Response to Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides (Dec. 29, 2016), EPA-HQ-OPP-2008-0316-0071, (submitted to docket EPA-HQ-OPP-2010-0119);
9. DAS Legal and Policy Comments on (i) EPA's Response to Comments Related to Applying the FQPA 10X Safety Factor for the Organophosphate Pesticides; (ii) Response to Occupational and Residential Exposure-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments; and (iii) Response to Dietary-Related Comments on the Preliminary Organophosphate Human Health Risk Assessments, (July 24, 2017) (submitted to docket EPA-HQ-OPP-2010-0119);

10. DAS Response to Objections to EPA's Denial of Petition to Revoke Tolerances and Cancel Registrations for Chlorpyrifos (and supporting Declarations), (Aug. 27, 2018) (submitted to docket EPA-HQ-OPP-2007-1005-0526);

11. Br. of Amicus Curiae Dow AgroSciences in Supp. of EPA, LULAC v. Wheeler, Nos. 19-71979, 19-71982 (9th Cir. Mar. 6, 2020), ECF No. 53-2;

12. D. Juberg and J. Driver, A Review of Recent Studies - Red Blood Cell Cholinesterase Inhibition as a Point of Departure for Regulation of Chlorpyrifos is Protective Against Neurodevelopmental Toxicity, (June 17, 2020) ("DAS Review of Recent Studies");

13. D. Juberg and J. Driver, Scientific Bases and Perspectives on Uncertainty and Safety Factors for Assessing Risks Associated with Human Chlorpyrifos Exposures, (June 17, 2020) ("DAS Submission on Uncertainty and Safety Factors");

14. A Study of Cholinesterase Inhibition in Peripheral Tissues in Sprague Dawley Rats Following Exposure to Chlorpyrifos Oxon in Drinking Water for 21 Days, MRID 51392601, submitted by Corteva Agriscience, and

15. Corteva Agriscience's Comments on Chlorpyrifos Proposed Interim Registration Review Decision (Feb. 2, 2021).

In the United States Court of Appeals
FOR THE EIGHTH CIRCUIT

No. 22-1422

RED RIVER VALLEY SUGARBEET GROWERS ASSOCIATION; U.S. BEET SUGAR ASSOCIATION; AMERICAN SUGARBEET GROWERS ASSOCIATION; SOUTHERN MINNESOTA BEET SUGAR COOPERATIVE; AMERICAN CRYSTAL SUGAR COMPANY; MINN-DAK FARMERS COOPERATIVE; AMERICAN FARM BUREAU FEDERATION; AMERICAN SOYBEAN ASSOCIATION; IOWA SOYBEAN ASSOCIATION; MINNESOTA SOYBEAN GROWERS ASSOCIATION; MISSOURI SOYBEAN ASSOCIATION; NEBRASKA SOYBEAN ASSOCIATION; SOUTH DAKOTA SOYBEAN ASSOCIATION; NORTH DAKOTA SOYBEAN GROWERS ASSOCIATION; NATIONAL ASSOCIATION OF WHEAT GROWERS; CHERRY MARKETING INSTITUTE; FLORIDA FRUIT AND VEGETABLE ASSOCIATION; GEORGIA FRUIT AND VEGETABLE GROWERS ASSOCIATION; NATIONAL COTTON COUNCIL OF AMERICA; AND GHARDA CHEMICALS INTERNATIONAL, INC.,

Petitioners,

v.

MICHAEL S. REGAN, ADMINISTRATOR, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY AND UNITED STATES ENVIRONMENTAL PROTECTION AGENCY,

Respondents.

On Petition for Review from the
U.S. Environmental Protection Agency

PETITIONERS' RENEWED MOTION FOR A PARTIAL STAY PENDING REVIEW

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INTRODUCTION

Petitioners seek to preserve critical uses of the insecticide chlorpyrifos that the Environmental Protection Agency ("EPA" or "the Agency") agrees are safe and provide great benefit to American agriculture. These uses pertain to eleven crops (alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugarbeet, strawberry, and wheat) in states where EPA concluded such use is safe ("EPA's Designated Safe Uses"). Att. 1, Ex. B (Proposed Interim Registration Review Decision, hereinafter "PID") at 40–41. The value of these crops to the U.S. economy surpasses $59 billion annually. Moreover, these eleven crops are critical to the livelihoods of the family farmers represented here.

Despite finding that EPA's Designated Safe Uses are safe for everyone, EPA issued a rule that prohibited *all* uses of chlorpyrifos for agricultural commodities. *See Final Rule for Chlorpyrifos Tolerance Revocations*, 86 Fed. Reg. 48,315 (Aug. 30, 2021) (the "Final Rule"), Declaration of Nash E. Long ("Long Decl.") Ex. A. EPA has denied Petitioners' objections to and requests to administratively stay the Final Rule ("EPA's Denial"). *Chlorpyrifos; Final Order Denying*

Objections, Requests for Hearings, and Requests for a Stay of the August 2021 Tolerance Final Rule, 87 Fed. Reg. 11,222 (Feb. 28, 2022), Long Decl. Ex. FF. EPA made clear in EPA's Denial that it "does not dispute its own scientific conclusions and findings" concerning EPA's Designated Safe Uses. 87 Fed. Reg. at 11,241. Rather, EPA attempted to justify prohibiting all uses, rather than limiting permissible uses to EPA's Designated Safe Uses, by claiming that it had an obligation under the Federal Food, Drug, and Cosmetic Act ("FFDCA") to make a decision considering all currently registered uses. *Id.*

That is not the law. EPA did not have to make one safety determination on the basis of all currently registered uses. The plain language of the FFDCA requires a tolerance-by-tolerance analysis for revocation—not a wholesale approach that ignores individual tolerances that EPA knows to be safe. 21 U.S.C. § 346a(b)(2)(A)(i) (EPA "shall modify or revoke *a* tolerance if the Administrator determines *it* is not safe") (emphasis added). EPA must base those safety determinations upon "anticipated" uses—not current uses. *Id.* § 346a(b)(2)(A)(ii). EPA regulates these pesticide uses under the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), and has a statutory obligation to

harmonize its registrations under FIFRA with its tolerance decisions under FFDCA. *Id.* § 346a(l)(1).

At its core, the Petition seeks review of a legal question, as EPA's Denial concedes: whether EPA's new interpretation of the FFDCA and FIFRA—requiring all registered uses of a pesticide to rise or fall together when considering the safety of tolerances—allows EPA to ignore its findings that certain uses and tolerances are safe. EPA had already done the work necessary to identify the tolerances that should be retained: EPA's Designated Safe Uses. The Agency should have followed its statutory duty and taken the steps necessary to preserve EPA's Designated Safe Uses and to oversee an orderly phase-out of all other food uses. Indeed, EPA held extensive talks with Petitioner Gharda to do just that. EPA then reversed course at the eleventh hour and made a wholesale revocation of all agricultural uses, contrary to its own science.

EPA's sweeping rule will cause significant and irreparable harm to the thousands of farmers represented here, who need chlorpyrifos to

fight insect infestation and preserve their crops.[1] In many cases, growers have no adequate substitute for controlling insects that attack their crops. Where alternatives exist, those insecticides are more expensive and less effective than chlorpyrifos. Without the ability to apply chlorpyrifos for EPA's Designated Safe Uses, crop yields will decrease and costs of production will increase. The resulting economic losses will be substantial. For example, over half of the domestic supply of sugar comes from sugarbeets grown by farmers represented by Petitioners Red River Valley Sugarbeet Growers Association, U.S. Beet Sugar Association, American Sugarbeet Growers Association, Southern Minnesota Beet Sugar Cooperative, American Crystal Sugar Company, and Minn-Dak Farmers Cooperative. Att. 1, Ex. F at 9. Petitioners

[1] Petitioners Red River Valley Sugarbeet Growers Association, U.S. Beet Sugar Association, American Sugarbeet Growers Association, Southern Minnesota Beet Sugar Cooperative, American Crystal Sugar Company, Minn-Dak Farmers Cooperative, American Farm Bureau Federation, American Soybean Association, Iowa Soybean Association, South Dakota Soybean Growers Association, National Association of Wheat Growers, Cherry Marketing Institute, Florida Fruit and Vegetable Association, Georgia Fruit and Vegetable Association, and National Cotton Council of America (hereinafter, the "Grower Petitioners") represent individual farmers and growers who collectively cover each of the eleven agricultural commodities for which EPA found the use of chlorpyrifos safe and of high benefit.

Southern Minnesota Beet Sugar Cooperative, American Crystal Sugar Company, and Minn-Dak Farmers Cooperative estimate that their members will suffer losses approaching $82 million per year under the Final Rule. Att. 2, Ex. F (Geselius Decl.) at ¶22; Att. 2, Ex. G (Hastings Decl.) at ¶20; Att. 2, Ex. I (Metzger Decl.) at ¶18. The crop losses EPA estimates will occur threaten the viability of the sugarbeet cooperatives here. Att. 2, Ex. G (Hastings Decl.) at ¶27. Losses suffered by individual sugarbeet farmers will be equally significant. For example, a sugarbeet grower (one of the 10,000 family farmers represented by the sugarbeet petitioners) estimates his farm will lose up to $400,000 annually under EPA's Final Rule. Att. 2, Ex. B (Baldwin Decl.) at ¶14. These harms are imminent, as farmers will need to apply chlorpyrifos beginning in April 2022 to control destructive pests. Att. 2, Ex. H (Haugrud Decl.) at ¶8. And these harms are certain, as EPA's own calculations show. PID at 42.

The Final Rule will also irreparably harm Gharda, the primary supplier of chlorpyrifos for agricultural use in the United States. The Final Rule will effectively deprive Gharda of its legally protectable property interest in its chlorpyrifos registration. It will also cause

Gharda significant unrecoverable economic losses and reputational harm from lost sales, lost investment in inventory, and customer and public ill-will.

Petitioners made these facts known to EPA, in written objections to the Final Rule and in requests for an administrative stay of its effective date.[2] EPA ignored these entreaties for over four months, then issued EPA's Denial rejecting them. EPA's Denial acknowledged the "cases for a stay" made by certain Petitioners "are not frivolous and are being pursued in good faith." 87 Fed. Reg. at 11,268.

Pursuant to Federal Rule of Appellate Procedure 18, to avoid irreparable harm, this Court should stay implementation of the rule with respect to EPA's Designated Safe Uses. This Court should also stay the tolerance expiration date for all other crop uses of chlorpyrifos until the Agency coordinates its action with FIFRA and provides an appropriate existing stocks order for those uses.

[2] All Petitioners except the National Cotton Council of America filed objections.

BACKGROUND

Chlorpyrifos, a broad-spectrum, organophosphate insecticide, has been registered for use in the United States since 1965 and is currently registered for use on food crops and in non-food use settings. 86 Fed. Reg. 48,315, 48,320 (Aug. 30, 2021). Grower Petitioners represent individual farmers, particularly in the upper Midwest, who rely on chlorpyrifos to fight destructive insects, to meet demand for their products, and to avoid significant crop losses. Chlorpyrifos is a critical tool—sometimes the only tool—for addressing several pest problems for the crops at issue. *See, e.g.*, Att. 2, Ex. G (Hastings Decl.) at ¶11; Att. 2, Ex. F (Geselius Decl.) at ¶12; Att. 2, Ex. J (Crittenden Decl.) at ¶¶10–15; Att. 2, Ex. Q (Schmitz Decl.) at ¶¶11–15.

EPA regulates the use of insecticides under the FFDCA and FIFRA. The FFDCA requires EPA to set food safety "tolerances" that represent the maximum levels of pesticide residues allowed in or on agricultural commodities. 21 U.S.C. § 346a. EPA "may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe" and "shall modify or revoke a tolerance if the Administrator determines it is

not safe." *Id.* § 346a(b)(2)(A)(i). When establishing, modifying, or revoking a tolerance, EPA must consider, among other things, "the validity, completeness, and reliability of the available data from studies of the pesticide chemical and pesticide chemical residue." *Id.* § 346a(b)(2)(D)(i).

The Food Quality Protection Act ("FQPA") amended the FFDCA to establish a safety standard for pesticide tolerances for residues in or on raw agricultural commodities. Such a tolerance is deemed "safe" if "there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information." *Id.* § 346a(b)(2)(A)(ii). This provision contemplates exposures from food, drinking water, and non-occupational exposure. When assessing "reasonable certainty [of] no harm," EPA applies an additional tenfold ("10X") margin of safety to take into account potential pre- and post-natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. *Id.* § 346a(b)(2)(C)(ii)(II). The Agency may apply a different margin of safety (e.g., a 1X safety factor) if there is "reliable data" to support doing so. *Id.*

FIFRA establishes a licensing or "registration" regime for regulating pesticide uses. 7 U.S.C. § 136a(a). In approving a pesticide registration, EPA must review and approve pesticide labeling, which governs its use. *Id.* § 136j(a)(2)(G). When revoking a tolerance for a pesticide chemical residue in or on food, the FFDCA requires EPA to "coordinate such action with any related necessary action under [FIFRA]." 21 U.S.C. § 346a(l)(1). That "related action" may include canceling the pesticide's registration and entry of an "existing stocks" order for "the continued sale and use of existing stocks of a pesticide whose registration is suspended or canceled." 7 U.S.C. § 136d(a), (b).

As described in the Final Rule, EPA's action came after years of administrative process and litigation surrounding EPA's established chlorpyrifos tolerances. In 2007, several nongovernmental organizations ("NGOs") petitioned EPA to revoke all existing chlorpyrifos tolerances. EPA issued an order denying the petition in 2017 and subsequently denied the NGOs' objections. *League of United Latin Am. Citizens v. Regan*, 996 F.3d 673, 680–90 (9th Cir. 2021) ("*LULAC*"). On April 29, 2021, the U.S. Court of Appeals for the Ninth Circuit vacated those denials and ordered EPA to "issue a final

regulation within 60 days following issuance of the mandate that either (a) revokes all chlorpyrifos tolerances or (b) modifies chlorpyrifos tolerances and simultaneously certifies that, with the tolerances so modified, the EPA has determined that there is a reasonable certainty that no harm will result." *Id.* at 703–04. The court further instructed that EPA "modify or cancel related FIFRA registrations for food use in a timely fashion." *Id.*

The court's order made clear that EPA could "choose to modify chlorpyrifos tolerances, rather than to revoke them," based on a safety determination. *Id.* at 702. In making this statement, the court was aware of the Agency's PID. *Id.* at 703. The court explained that "[i]f, based upon the EPA's further research the EPA can now conclude to a reasonable certainty that modified tolerances or registrations would be safe, then it may modify chlorpyrifos registrations rather than cancelling them." *Id.* In discussions in May and June 2021, EPA expressed to Gharda its willingness to consider retaining EPA's Designated Safe Uses, and Gharda committed to accept a narrowing of its registration consistent with the Agency's safety finding. Seethapathi Decl. ¶¶ 21–33. EPA then abruptly ceased discussion. *Id.* at ¶ 34.

On August 30, 2021, EPA issued the Final Rule, revoking all tolerances for chlorpyrifos. 86 Fed. Reg. at 48,315. The Final Rule stated that "given the currently registered uses of chlorpyrifos, EPA cannot determine there is a reasonable certainty that no harm will result from aggregate exposure to residues, including all dietary (food and drinking water) exposures and all other exposures for which there is reliable information," notwithstanding the FQPA 10X safety factor. *Id.* at 48,317.

Applying the conservative 10X safety factor, EPA confirmed key findings from its PID—namely that there are no risk concerns based on exposures to chlorpyrifos from food alone. Factoring in drinking water exposures, EPA found that risks exceeded safe levels when taking into account all registered uses, but are within safe limits assuming only EPA's Designated Safe Uses. *Id.*

EPA conducted a drinking water assessment (DWA) in 2016 based on modeling all registered uses. *Id.* at 48,330. EPA conducted a refined 2020 DWA to better account for variability and estimate regional and watershed concentrations. 86 Fed. Reg. at 48,332. The 2020 DWA

underwent peer review,[3] and focused on a "subset of uses [(EPA's Designated Safe Uses)] . . . to determine, if these were the only uses permitted on the label, whether or not the resulting estimated drinking water concentrations" would be safe. 86 Fed. Reg. at 48,331. The results indicated that exposures for EPA's Designated Safe Uses were below the level of concern. *Id.*

EPA's Final Rule nevertheless put aside the 2020 DWA's results because, in EPA's view, "the Agency is required to assess aggregate exposure from all anticipated dietary, including food and drinking water, as well as residential exposure," and the 2020 drinking water assessment cannot be used to support "currently labeled uses." 86 Fed. Reg. at 48,333. EPA thus decided that, rather than maintain the tolerances for uses of chlorpyrifos it found safe, it should revoke all of them.

Petitioners filed objections to EPA's decision and requested a stay of the Final Rule, which EPA denied on February 22, 2022. Long Decl.,

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[3] *See generally* U.S. EPA, Memorandum, Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review, EPA-HQ-OPP-2008-0850-0941 (Sept. 15, 2020), https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0941.

Att. 1, Ex. FF. Petitioners exhausted all administrative means of staying the Final Rule, which took effect on February 28, 2022. The 2022 growing season, and the need for farmers to use chlorpyrifos in planting and protecting their crops, beginning in mid-April, is quickly approaching. Att. 2, Ex. H (Haugrud Decl.) at ¶8. Without a stay of the Final Rule as requested herein, Petitioners will suffer immediate and ongoing irreparable harm from the inability to sell and use chlorpyrifos.

ARGUMENT

Courts consider four factors in determining whether to stay agency action pending judicial review: (1) the applicant's likelihood of success on the merits; (2) irreparable injury absent a stay; (3) the balance of equities among interested parties; and (4) the public interest. *Nken v. Holder*, 556 U.S. 418, 434 (2009); *accord Home Instead, Inc. v. Florance*, 721 F.3d 494, 497 (8th Cir. 2013) (quoting *Dataphase Sys., Inc. v. C L Sys., Inc.,* 640 F.2d 109, 113 (8th Cir. 1981) (en banc)). Although "no single factor is determinative," *Dataphase Sys.*, 640 F.2d at 113, "the 'likelihood of success on the merits is most significant,'" *Barrett v. Claycomb*, 705 F.3d 315, 320 (8th Cir. 2013) (quoting *S.J.W. ex rel. Wilson v. Lee's Summit R-7 School Dist.*, 696 F.3d 771, 776 (8th

Cir. 2012)). Petitioners satisfy these factors for a stay of the revocation of the tolerances for EPA's Designated Safe Uses and, for all other crop uses, a stay of the revocation until EPA issues an appropriate existing stocks order.

I. Petitioners Are Likely to Succeed in Challenging EPA's Unlawful Decision to Revoke the Tolerances For the Crop Uses EPA Found Safe.

This Court must set aside agency action if it is "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706. Agency action is arbitrary and capricious if

> [1] the agency has relied on factors which Congress has not intended it to consider, [2] entirely failed to consider an important aspect of the problem, [3] offered an explanation for its decision that runs counter to the evidence before the agency, or [4] is so implausible that it could not be ascribed to a difference in view or the product of agency expertise.

Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto. Ins. Co., 463 U.S. 29, 43 (1983); *accord Nebraska v. EPA*, 812 F.3d 662, 666 (8th Cir. 2016).

EPA's decision to revoke tolerances for EPA's Designated Safe Uses is arbitrary and capricious and contrary to law for at least three reasons. First, EPA ignored the plain text of the FFDCA and FIFRA, rendering its decision contrary to law. Second, EPA's explanation for

its decision runs counter to its own finding that the tolerances for EPA's Designated Safe Uses are safe. Finally, EPA ignored important aspects of the problem in issuing the Final Rule, including Petitioners' reliance interests and the need for harmonization with FIFRA.

A. EPA ignored the plain text of the FFDCA and FIFRA in reaching its decision.

The FFDCA specifies how EPA must approach decisions concerning tolerances. For insecticides such as chlorpyrifos, EPA has established multiple tolerances: a separate one for each agricultural commodity on which it may be used. The plain language of the FFDCA specifies a tolerance-by-tolerance examination by EPA of these separate safety standards in determining whether to leave it in place, to modify it, or to revoke it. EPA "may establish or leave in effect *a tolerance* . . . if the Administrator determines that *the tolerance* is safe . . . [and] shall modify or revoke *a tolerance* if the Administrator determines *it* is not safe." 21 U.S.C. § 346a(b)(2)(A)(i) (emphasis added). This plain language requires that a determination on the safety of a tolerance occur on an individual basis.

Once EPA has made its safety decisions for the existing tolerances, then FFDCA and FIFRA require EPA to modify or cancel

the FIFRA registrations accordingly. *See* 21 U.S.C. § 346a(l)(1) ("[T]he Administrator shall coordinate such action with any related necessary action under [FIFRA]."). In short, FFDCA and FIFRA required EPA to address chlorpyrifos tolerances on a tolerance-by-tolerance basis—revoking any chlorpyrifos tolerances where it could not make a safety finding, leaving in place the tolerances for the eleven uses EPA found safe, or modifying individual tolerances as the science would require—and then cancel or modify chlorpyrifos registrations under FIFRA in accordance with that science. This is precisely how EPA has applied the law previously, Seethapathi Decl. Ex. 4, Reiss Decl. at ¶17, consistent with FFDCA's forward-looking mandate to consider "anticipated" uses in making a safety decision. 21 U.S.C. § 346a(b)(2)(A)(i).

EPA had already done the work in the PID to identify the tolerances to be maintained: EPA's Designated Safe Uses. Instead of following the science and adjusting the registrations to conform to its safety findings, EPA concluded—contrary to the plain language of FIFRA—that it could not do so. EPA asserted, for the first time, that all "currently registered" uses had to rise or fall together. EPA had no

basis for fashioning this new rule, and the Final Rule and EPA's Denial claim none.

At most, EPA suggests that the Ninth Circuit's order mandated this approach. 86 Fed. Reg. at 48,316. That argument fails. EPA had already drawn the necessary lines in the 2020 PID, identifying for retention EPA's Designated Safe Uses. Citing the PID, the Ninth Circuit gave EPA 60 days to make its decision to modify or revoke chlorpyrifos tolerances on the basis of the available evidence. With the science already in hand, EPA had more than enough time to "act based upon the evidence" as required by the Ninth Circuit's order. *Id.* at 703. EPA's Denial confirms that EPA does not dispute its conclusions that EPA's Designated Safe Uses are in fact safe.

Because EPA's decision-making departed from the plain language of FFDCA and FIFRA, as well as the agency's own settled practice, EPA's Final Rule is contrary to law and must be set aside.

B. EPA's explanation for its decision runs counter to its own safety findings.

The Final Rule and EPA's Denial are arbitrary and capricious because they runs counter to the evidence in the record, including EPA's own safety findings. EPA acknowledged as much in the Final

Rule, 86 Fed. Reg. at 48,333, and again in EPA's Denial, 87 Fed. Reg. at 11,241. EPA's Final Rule explained that the "PID recognized that there might be limited combinations of uses in certain geographic areas that could be considered safe." 86 Fed. Reg. at 48,333 (citing PID at 40 (discussing EPA's Designated Safe Uses)). Indeed, the PID explained that EPA's Designated Safe Uses "will not pose potential risks of concern" and at least these uses could be retained. PID at 40. EPA's Denial confirmed that EPA "does not dispute" these conclusions. 87 Fed. Reg. at 11,241.

EPA nevertheless refused to apply its own scientific findings and instead decided to revoke all of the tolerances, including those for EPA's Designated Safe Uses. EPA's Denial upheld the Final Rule's claim that EPA could not modify chlorpyrifos labels under FIFRA to narrow permissible uses. 86 Fed. Reg. at 48,333; 87 Fed. Reg. at 11,237–38. EPA also claimed that it could not make a safety finding for a narrowed subset of uses unless "EPA has a reasonable basis to believe" that other uses will cease. 87 Fed. Reg. at 11,246.

EPA fails to explain why it could not make label changes consistent with its safety finding. 86 Fed. Reg. at 48,320–33; 87 Fed.

Reg. at 11,238. EPA had the time and ability to do just that, as its negotiations with Gharda prior to the Final Rule demonstrate. No data review would have been required: EPA had already made the safety finding months earlier.[4] EPA and Gharda had already discussed, for several weeks, registration and label modifications. Gharda had already agreed to cancellation of the registrations for everything but EPA's Designated Safe Uses. Seethapathi Decl. ¶ 24. EPA has offered no genuine basis for ignoring its safety findings supporting retention of EPA's Designated Safe Uses. Its decision is therefore arbitrary and capricious. *See Siddiqui v. Holder*, 670 F.3d 736, 744 (7th Cir. 2012) (agency use of "only generalized language to reject the evidence" is improper).

Courts have rejected similarly overbroad agency actions where the agency ignored its own science. For example, the D.C. Circuit rejected EPA's revocation of import tolerances for carbofuran where EPA had acknowledged that the imported foods were safe. *Nat'l Corn Growers*

[4] Label changes with data review generally take four months, but that would not be necessary here. *See* EPA, PRIA Fee Category Table – Registration Division – Amendments, last visited January 19, 2022, https://www.epa.gov/pria-fees/pria-fee-category-table-registration-division-amendments.

Ass'n v. EPA, 613 F.3d 266 (D.C. Cir. 2010). Likewise, this Court rejected agency action where the weight of the evidence went against the agency's decision. *Sugule v. Frazier*, 639 F.3d 406, 412 (8th Cir. 2011). Here, EPA's action was similarly arbitrary and capricious because EPA ignored its own science and provided an unsupported justification for its decision.

C. EPA failed to consider important aspects of the problem.

EPA's decision is also arbitrary and capricious because EPA failed to consider important aspects of the problem. *See Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43. First, EPA failed to consider Petitioners' significant reliance interests. "When an agency changes course, . . . it must 'be cognizant that longstanding policies may have engendered serious reliance interests that must be taken into account.'" *Dep't of Homeland Sec. v. Regents of the Univ. of California*, 140 S. Ct. 1891, 1913 (2020) (quoting *Encino Motorcars, LLC v. Navarro*, 136 S. Ct. 2117, 2126 (2016)). The agency is "required to assess whether there were reliance interests, determine whether they were significant, and weigh any such interests against competing policy concerns." *Id.* at 1915.

Grower Petitioners have a significant reliance interest in the EPA-approved use of chlorpyrifos as a safe and effective insecticide for protecting their crops. EPA failed to consider the interests of the farmers who have relied on chlorpyrifos for decades to grow a number of agricultural commodities safely. Similarly, Gharda has a reliance interest in EPA following the science in making decisions that impact Gharda's investment in its registration. EPA failed to consider this interest as well. EPA's overbroad decision upended decades of approved chlorpyrifos use, when EPA could lawfully, and based on its own science, leave in effect the tolerances for EPA's Designated Safe Uses.

EPA also failed to consider the need for an existing stocks order for crop uses other than EPA's Designated Safe Uses. EPA has a statutory mandate under FIFRA to ensure the safe, lawful, and orderly phase-out of these products. Yet EPA failed to do this in coordination with the Final Rule. *See* 86 Fed. Reg. 48,315. EPA's failure to deal with the issue of existing stocks of chlorpyrifos causes substantial harm, and further demonstrates that its Final Rule was arbitrary and capricious.

II. Petitioners Will Suffer Irreparable Harm Absent a Partial Stay As Requested Herein.

To demonstrate irreparable harm, "a party must show that the harm is certain and great and of such imminence that there is a clear and present need for equitable relief." *Iowa Utils. Bd. v. FCC*, 109 F.3d 418, 425 (8th Cir. 1996). The threat of unrecoverable economic loss qualifies as irreparable harm. *Id.* at 426. Economic losses are unrecoverable where the injured party would not be able to bring a lawsuit to recover their economic losses if agency rules are eventually overturned. *Id.* Further, the "potential loss of consumer goodwill qualifies as irreparable harm." *Id.*; *see also Med. Shoppe Int'l, Inc. v. S.B.S. Pill Dr., Inc.*, 336 F.3d 801, 805 (8th Cir. 2003) (loss of reputation and goodwill constitute irreparable injury).

Chlorpyrifos is a critical tool for which "there is no equal replacement," and in some cases, no replacement at all. *See, e.g.*, Att. 2, Ex. T (Harris Decl.) at ¶8. For example, chlorpyrifos is "the only tool that is consistently effective in controlling destructive pests" for sugarbeets. Att. 2, Ex. F (Geselius Decl.) at ¶12; *see also* Att. 2, Ex. A (Weber Decl.) at ¶8; Att. 2, Ex. B (Baldwin Decl.) at ¶10. As a result, loss of chlorpyrifos will have "a devastating impact," including up to

$400,000 in annual losses to just one family farm. Att. 2, Ex. B (Baldwin Decl.) at ¶¶11, 14. As another grower explained, due to the lack of alternatives, "our only plan is to hope that there is not a significant pest problem." Att. 2, Ex. H (Haugrud Decl.) at ¶9. These impacts are industry-wide, impacting over 10,000 family farmers. For example, without the ability to use chlorpyrifos, the three farming cooperative Petitioners estimate unrecoverable losses for their sugarbeet grower members approaching $82 million per year. *See* Att. 2, Ex. G (Hastings Decl.) at ¶¶20-21; Att. 2, Ex. F (Geselius Decl.) at ¶22; Att. 2, Ex. I (Metzger Decl.) at ¶18. The Final Rule threatens the viability of these businesses. Att. 2, Ex. G (Hastings Decl.) at ¶27.

Similar issues exist with other crops at issue here. For example, a peach grower represented by Petitioners has been unable, after six years, to find an effective alternative to fight the lessor peach tree borer. Att. 2, Ex. J (Crittenden Decl.) at ¶14. Chlorpyrifos is also the only effective insecticide to protect against trunk borers in cherry trees. Att. 2, Ex. T (Harris Decl.) at ¶10; *see also* Att. 2, Ex. J (Crittenden Decl.) at ¶15. When a tree is lost to trunk borers, it can take up to ten

years to get a replacement tree into production. Att. 2, Ex. T (Harris Decl.) at ¶12.

Even where alternatives exist, losing chlorpyrifos causes significant problems because of pesticide resistance. *See, e.g.*, Att. 2, Ex. K (Scott Decl.) at ¶¶9–11; Att. 2, Ex. Q (Schmitz Decl.) at ¶¶11–16; Att. 2, Ex. R (Johnson Decl.) at ¶¶9–16. "If growers have fewer tools to rotate and mix as a result of losing chlorpyrifos, the effectiveness of the remaining tools will erode more quickly as pest populations develop resistance." Att. 2, Ex. Q (Schmitz Decl.) at ¶14; Att. 2, Ex. J (Crittenden Decl.) at ¶12 (pesticide resistance is "a serious problem"). For example, alternatives for controlling soybean pests are limited. Loss of chlorpyrifos "would result in a rapid buildup of insecticide resistance to the other remaining options." Att. 2, Ex. Q (Schmitz Decl.) at ¶¶11–16. This will have "devastating economic impacts" for soybean farms, Att. 2, Ex. L (Goblish Decl.) at ¶13, including an estimated $1.26 million in annual cost increases, Att. 2, Ex. K (Scott Decl.) at ¶13, due to the loss of chlorpyrifos.

A partial stay is needed now because these losses will occur before litigation concludes. As one grower explained, "pest infestation will be

worse on my farm in 2023 if chlorpyrifos cannot be used during the spring of 2022." Att. 2, Ex. B (Baldwin Decl.) at ¶12. These losses are unrecoverable should the Final Rule be overturned. *See Iowa Utils. Bd.*, 109 F.3d at 426. Also, these growers are likely to suffer loss of customer trust because "EPA also attacked the safety of prior uses of chlorpyrifos in the eyes of the public." Att. 2, Ex. A (Weber Decl.) at ¶19; *see also* Att. 2, Ex. C (Bladow Decl.) at ¶22; Att. 2, Ex. I (Metzger Decl.) at ¶20. Such reputational harm is irreparable. *See Iowa Utils. Bd.*, 109 F.3d at 426.

Gharda will also suffer irreparable harm from revocation of tolerances, effectively causing the loss of its EPA registration for chlorpyrifos, in which it has a legally protectable property interest. *See Reckitt Benckiser Inc. v. EPA,* 613 F.3d 1131, 1133 (D.C. Cir. 2010) ("A FIFRA registration is a product-specific license describing the terms and conditions under which the product can be legally distributed, sold, and used."); *see also Blackman v. District of Columbia*, 277 F. Supp. 2d 71, 79 (D.D.C. 2003) (due process violations constitute irreparable injury). Revocation of all tolerances will also cause Gharda devastating economic and reputational harm from lost sales, lost investment in

significant quantities of existing inventory it is unable to exhaust, and customer and public ill-will. Seethapathi Decl. ¶¶46–51.

III. The Public Interest and Balance of the Equities Support a Partial Stay.

The public interest and the balance of the equities support Petitioners' request for a stay. The partial stay requested will provide critical relief to the family farms that will be significantly harmed by the Final Rule. *Supra* at 21-25. Further, the agricultural commodities grown by the farmers represented here contribute significantly to the U.S. economy as a whole and to local communities in particular. *See, e.g.*, Att. 2, Ex. F (Geselius Decl.) at ¶7 (sugarbeet farming has a $4.9 billion impact in Minnesota and North Dakota). Thus, the losses suffered by Petitioners and the farmers represented will be magnified and spread to connected parts of the farming economy and beyond. *Id*.

Public health and public interest considerations do not outweigh the need for a partial stay. As EPA's Denial confirms, EPA's Designated Safe Uses present no concerns for food safety or public health. *Supra* at 18. The weighing of the public interest supports a stay based on the substantial, irreparable economic harm to growers, to Gharda, and to the public absent the stay requested herein.

CONCLUSION

This Court should stay EPA's decision revoking the tolerances for EPA's Designated Safe Uses, pending judicial review of that decision. This Court should also stay the tolerance expiration date for all other crop uses, until the Agency provides an appropriate existing stocks order for those uses.

March 3, 2022

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Petitioners' Renewed Motion for Partial Stay Pending Review complies with the type-volume limitation of Federal Rule of Appellate Procedure because it contains 5,199 words. This Motion complies with the typeface and the type style requirements of Federal Rule of Appellate Procedure 27 because this brief has been prepared in a proportionally spaced typeface using Word 14-point Century Schoolbook typeface.

Dated: March 3, 2022

s/ Nash E. Long
Nash E. Long

CERTIFICATE OF SERVICE

I hereby certify that on March 3, 2022, I electronically filed the foregoing Petitioners' Renewed Motion for Partial Stay Pending Review with the Clerk of the Court for the United States Court of Appeals for the Eighth Circuit by using the CM/ECF system, which will send a notice of electronic filing to all parties on the electronic filing receipt.

I also hereby certify that I have, on this day, served by overnight mail a copy of the foregoing document upon the parties below.

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