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Memorandum

To: Stephanie Paige and Rose Kachadoorian, Oregon Department of Agriculture

From: David Farrer, Ph.D. Toxicologist

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Subject: Follow-up discussion on points raised in May 27, 2020 Oregon Chlorpyrifos Workgroup - chlorpyrifos neurodevelopmental toxicity and EPA and California EPA risk assessment findings

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The purpose of this memorandum is to follow up on some questions raised by workgroup participants during the May 27, 2020 meeting of the Oregon Chlorpyrifos Workgroup hosted by the Oregon Department of Agriculture (ODA). During my presentation on the acute and chronic health effects of exposure to chlorpyrifos, workgroup members raised questions about the U.S. Environmental Protection Agency's (EPA's) position on some of the scientific evidence I referenced during my talk. Workgroup members also asked why the Oregon Health Authority (OHA) disagrees with some assertions and conclusions the EPA has made about the robustness and usability of some of the existing scientific evidence.

Background

The regulatory history of chlorpyrifos is long and complex. The portion of that history relevant to my presentation in the meeting and the questions addressed here runs from the publication of EPA's 2016 risk assessment on chlorpyrifos[1] to EPA's July 2019 order[2] denying a petition to revoke all tolerances and cancel all registrations for the insecticide chlorpyrifos. Had EPA approved the petition, it would have had the practical effect of banning the chemical from commerce.

The 2016 EPA risk assessment showed that nearly all uses and applications of chlorpyrifos posed unacceptable risk based on its potential to cause neurodevelopmental toxicity in exposed children. Subsequently, in 2017 and again in 2019[2], the EPA issued orders denying petitions to ban chlorpyrifos. Such a ban would be supported by the findings of EPA's own 2016 risk assessment[1]. The questions raised in the workgroup meeting were related to why OHA disagrees with the rationale that the EPA presented in its 2017 and 2019 orders to justify their denial of the petitions that would have effectively banned chlorpyrifos. Those are the questions OHA will address in this memo.

EPA's 2017 and 2019 orders[2] do not dispute that chlorpyrifos causes neurodevelopmental toxicity following in utero or early life exposure. From the bottom of page 30 of the EPA's 2019 denial order:

> "EPA has, since the issuance of the 2006 RED, consistently concluded that the available data support a conclusion of increased sensitivity of the young to the neurotoxic effects of chlorpyrifos and for the susceptibility of the developing brain to chlorpyrifos. This conclusion comes from an evaluation across multiple lines of evidence including mechanistic studies and newer *in vivo* laboratory animal studies, but particularly with the available epidemiology reports along with feedback from the 2012 and 2016 FIFRA SAP meetings."[2]

OHA agrees with the EPA on this conclusion. The questions EPA has cited in 2017 and 2019 orders are not about whether chlorpyrifos causes developmental neurotoxicity, but rather the dose at which it occurs and the suitability of available scientific evidence to determine that dose.

EPA has not presented any new scientific evidence since the 2016 risk assessment that contradict the findings of that assessment related to dose. In fact, since the publication of that assessment, five animal studies[3–7] have been published supporting the findings of that 2016 risk assessment. California's Environmental Protection Agency (CalEPA) used those five animal studies as the basis for their 2018 risk assessment,[8] which came to similar conclusions to EPA's 2016 risk assessment about unacceptable risk.

In its 2017 and 2019 denial orders[2], EPA expressed three concerns about the existing dose-related scientific data that its 2016 risk assessment[1] used to develop a point of departure (POD). A POD is the dose found in human or animal studies that agencies use downstream in the risk assessment process to calculate the risk of health effects. EPA's three stated concerns are:

1. "the absence of a clear mechanism of action for chlorpyrifos in the developing brain"
2. "the dosing regimen in *in vivo* [animal] studies that differs from internationally accepted protocols"
3. "the lack of any meaningful raw data from the epidemiologic data that are the centerpiece of this area of inquiry"

The Oregon Health Authority (OHA) analysis below responds to each stated concern separately.

The absence of a clear mechanism of action for chlorpyrifos in the developing brain

There are many examples where EPA has regulated chemicals based on a clearly defined adverse health outcome despite inconclusive information about the specific toxicological mechanism by which those outcomes are brought about. Lead has been regulated for decades, despite the fact that even today there is not a scientific consensus on which of the proposed mechanisms of action drives the well-documented neurotoxicity.[9] A full understanding of an underlying mechanism of action driving an adverse health effect should not be necessary to select a POD if that POD is based on a well-documented adverse health outcome. EPA rightly began regulating lead before many of the currently hypothesized toxicological mechanisms driving neurotoxicity had been published.

EPA's 2019 denial order claims that an understanding of this mechanism of action is necessary to "reliably assess potential differences (and similarities) between laboratory animals and humans with respect to dose-response and temporal windows of susceptibility. In the absence of this information, EPA has no valid or reliable ways to bridge the scientific interpretation of the laboratory studies and epidemiology studies with chlorpyrifos."

EPA has acknowledged the scientific evidence published in peer-reviewed literature that neurodevelopmental effects of chlorpyrifos are observed in both humans and animals with good information about the doses leading to those effects. This is all that is necessary to derive a POD as the EPA's 2016 risk assessment did.

The dosing regimen in *in vivo* [animal] studies that differs from internationally accepted protocols

This concern posits that because dosing regimens in some animal studies are different from those typically used in larger, more standardized studies, EPA is unable to use those studies to determine the

alignment between animals and humans in terms of the precise timing of exposure during development that could result in the observed health outcome.

It is not necessary to understand the precise window of greatest sensitivity to chlorpyrifos, or how those windows may differ between animals and humans in order to select a POD. The critical data in question comes from epidemiological studies in exposed humans. In practice no one can, nor should they need to, predict which stage of pregnancy a woman is in during her inadvertent exposure to chlorpyrifos. It is public health best practice to protect vulnerable populations, such as fetuses, when there is clear evidence of harm to health, in this case from women's exposure to chlorpyrifos, during any point in pregnancy.

The lack of any meaningful raw data from the epidemiologic data that are the centerpiece of this area of inquiry

EPA has advanced in other forums that all raw data should be fully and publicly available. While that is a goal that scientists generally aim for, public availability does not make data inherently more valid than protected data.

There are valid reasons raw data from some epidemiological studies are protected. In many cases the raw data include personally identifiable information about study participants. Researchers are under legal and ethical obligations not to release information that could compromise the privacy of study participants. It is OHA's position that it does not make sense for EPA to disregard well-designed, important epidemiological studies simply because the private health data cannot be made public.

Federal agencies and many peer-review journals are developing and piloting databases that allow for efficient de-identification and sharing of raw data. This means that more epidemiological studies will be able to release non-identifiable raw data publicly for independent analysis in the future. However, it is very difficult for researchers to go back and de-identify large data sets that were not organized using these newer tools.

Updating Critical Endpoint Based on the Weight of Current Scientific Evidence

Traditionally, agencies like the EPA have used inhibition of an enzyme called acetylcholinesterase (AChE) as the critical endpoint for development of PODs when evaluating organophosphate (OP) insecticides like chlorpyrifos. Laboratory animal studies have demonstrated that at certain doses, chlorpyrifos can indeed cause a 10% red blood cell (RBC) AChE inhibition.[10] However, EPA's FIFRA Scientific Advisory Panel (SAP) has encouraged the agency to consider alternative methods for assessing chlorpyrifos health risk, including the use of epidemiological studies, since at least the 2012[11] release of EPA's own draft "Framework for Incorporating Human Epidemiological and Incident Data in Health Risk Assessment," which was favorably reviewed by the SAP[12]. In minutes from a 2012 SAP meeting,[13] the SAP encouraged EPA to "…consider whether AChE inhibition represents the critical marker for derivation of points of departure for chronic studies" because "…the neurodevelopmental effects may be independent of AChE inhibition." EPA's 2016 risk assessment represents the agency's efforts to comply with advice from its expert advisory panel. The concept of using a health effect other than AChE inhibition for chlorpyrifos is not new, and science-based agencies like the EPA are expected to adapt their methodology to follow the latest science rather than follow past practices for the sake of tradition.

References

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9. ATSDR - Toxicological Profile: Lead (page 179). https://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=96&tid=22.

10. See *Revocations*, 80 Fed. Reg. 69087 – 69090

11. This document was finalized in 2016 and is available here https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf

12. The Federal Insecticide, Fungicide, and Rodenticide Act, 7 U.S.C. §§ 136 – 136y.

13. Available at https://www.epa.gov/sites/production/files/2015-06/documents/041012minutes.pdf