

(2) Tolerances are established for residues of thiabendazole, including its metabolites and degradates, in or on the commodities in table 2 to paragraph (a)(2). Compliance with the tolerance

levels specified to table 2 to paragraph (a)(2) is to be determined by measuring only the sum of thiabendazole (2-(4-thiazolyl)benzimidazole) and its metabolite 5-hydroxythiabendazole (free

and conjugated) calculated as the stoichiometric equivalent of thiabendazole, in or on the commodity.

TABLE 2 TO PARAGRAPH (a)(2)

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ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 180

[EPA-HQ-OPP-2021-0523; FRL-5993-04-OCSPP]

Chlorpyrifos; Tolerance Revocations

AGENCY: Environmental Protection Agency (EPA).

ACTION: Final rule.

SUMMARY: On April 29, 2021, the United States Court of Appeals for the Ninth Circuit ordered EPA to issue a final rule concerning the chlorpyrifos tolerances by August 20, 2021. Based on the currently available data and taking into consideration the currently registered uses for chlorpyrifos, EPA is unable to conclude that the risk from aggregate exposure from the use of chlorpyrifos meets the safety standard of the Federal Food, Drug, and Cosmetic Act (FFDCA). Accordingly, EPA is revoking all tolerances for chlorpyrifos.

DATES: This final rule is effective October 29, 2021. The tolerances for all commodities expire on February 28, 2022.

Written objections, requests for hearings, or requests for a stay identified by the docket identification (ID) number EPA-HQ-OPP-2021-0523 must be received on or before October 29, 2021, and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I.C. of the

SUPPLEMENTARY INFORMATION unit in this document).

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2021-0523, is available at <http://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 public health concerns related to COVID-19, the EPA/DC and Reading

Room are 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 <http://www.epa.gov/dockets>.

FOR FURTHER INFORMATION CONTACT: Elissa Reaves, Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave. NW, Washington, DC 20460-0001; telephone number: 703-347-0206; email address: OPPChlorpyrifosInquiries@epa.gov.

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this action apply to me?

You may be potentially affected by this action if you are an agricultural producer, food manufacturer, or pesticide manufacturer. The following list of North American Industrial Classification System (NAICS) codes is not intended to be exhaustive, but rather provides a guide to help readers determine whether this document applies to them. Potentially affected entities may include:

- Crop production (NAICS code 111).
- Animal production (NAICS code 112).
- Food manufacturing (NAICS code 311).
- Pesticide manufacturing (NAICS code 32532).

Other types of entities not listed in this unit could also be affected. The NAICS codes have been provided to assist you and others in determining whether this action might apply to certain entities. To determine whether you or your business may be affected by this action, you should carefully examine the applicability provisions in Unit II. If you have any questions regarding the applicability of this action to a particular entity, consult the contact listed under **FOR FURTHER INFORMATION CONTACT**.

B. How can I get electronic access to other related information?

You may access a frequently updated electronic version of 40 CFR part 180 through the Government Printing Office's e-CFR site at http://www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl.

www.ecfr.gov/cgi-bin/text-idx?&c=ecfr&tpl=/ecfrbrowse/Title40/40tab_02.tpl.

C. How can I file an objection or hearing request?

Under FFDCA section 408(g), 21 U.S.C. 346a, any person may file an objection to any aspect of this regulation and may also request a hearing on those objections. You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2021-0523 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing and must be received by the Hearing Clerk on or before October 29, 2021. Addresses for mail and hand delivery of objections and hearing requests are provided in 40 CFR 178.25(b), although at this time, EPA strongly encourages those interested in submitting objections or a hearing request, to submit objections and hearing requests electronically. See Order Urging Electronic Service and Filing (April 10, 2020), https://www.epa.gov/sites/production/files/2020-05/documents/2020-04-10_-_order_urging_electronic_service_and_filing.pdf. At this time, because of the COVID-19 pandemic, the judges and staff of the Office of Administrative Law Judges (OALJ) are working remotely and not able to accept filings or correspondence by courier, personal deliver, or commercial delivery, and the ability to receive filings or correspondence by U.S. Mail is similarly limited. When submitting documents to the U.S. EPA OALJ, a person should utilize the OALJ e-filing system, at https://yosemite.epa.gov/OA/EAB/EAB-ALJ_upload.nsf.

Although EPA's regulations require submission via U.S. Mail or hand delivery, EPA intends to treat submissions filed via electronic means as properly filed submissions during this time that the Agency continues to maximize telework due to the pandemic; therefore, EPA believes the preference for submission via electronic means will not be prejudicial. If it is

impossible for a person to submit documents electronically or receive service electronically, *e.g.*, the person does not have any access to a computer, the person shall so advise OALJ by contacting the Hearing Clerk at (202) 564-6281. If a person is without access to a computer and must file documents by U.S. Mail, the person shall notify the Hearing Clerk every time it files a document in such a manner. The address for mailing documents is U.S. Environmental Protection Agency, Office of Administrative Law Judges, Mail Code 1900R, 1200 Pennsylvania Ave. NW, Washington, DC 20460.

In addition to filing an objection or hearing request with the Hearing Clerk as described in 40 CFR part 178 and above, please submit a copy of the filing (excluding any Confidential Business Information (CBI)) for inclusion in the public docket. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit the non-CBI copy of your objection or hearing request, identified by docket ID number EPA-HQ-OPP-2021-0523, using the Federal eRulemaking Portal at <http://www.regulations.gov>. Follow the online instructions for submitting comments. Do not submit electronically any information you consider to be CBI or other information whose disclosure is restricted by statute.

If you would like to submit CBI with your hearing request, please first contact the Pesticide Re-Evaluation Division by telephone, 703-347-0206, or by email address: OPPChlorpyrifosInquiries@epa.gov. Do not submit CBI to EPA through the Federal eRulemaking Portal or email.

D. What can I do if I want the Agency to maintain a tolerance that the Agency has revoked?

Any affected party has 60 days from the date of publication of this order to file objections to any aspect of this order with EPA and to request an evidentiary hearing on those objections (21 U.S.C. 346a(g)(2)). A person may raise objections without requesting a hearing.

The objections submitted must specify the provisions of the regulation deemed objectionable and the grounds for the objection (40 CFR 178.25). While 40 CFR 180.33(i) indicates a fee is due with each objection, EPA currently cannot collect such fees per 21 U.S.C. 346a(m)(3). If a hearing is requested, the objections must include a statement of the factual issue(s) on which a hearing is requested, the requestor's contentions on such issues, and a summary of any evidence relied upon by the objector (40 CFR 178.27).

Although any person may file an objection, EPA will not consider any legal or factual issue presented in objections, if that issue could reasonably have been raised earlier in the Agency's review of chlorpyrifos relative to this petition. Similarly, if you fail to file an objection to an issue resolved in the final rule within the time period specified, you will have waived the right to challenge the final rule's resolution of that issue (40 CFR 178.30(a)). After the specified time, issues resolved in the final rule cannot be raised again in any subsequent proceedings on this rule. See *Nader v EPA*, 859 F.2d 747 (9th Cir. 1988), cert denied 490 U.S. 1931 (1989).

EPA will review any objections and hearing requests in accordance with 40 CFR 178.30, and will publish its determination with respect to each in the **Federal Register**. A request for a hearing will be granted only to resolve factual disputes; objections of a purely policy or legal nature will be resolved in the Agency's final order, and will only be subject to judicial review pursuant to 21 U.S.C. 346a(h)(1), (40 CFR 178.20(c) and 178.32(b)(1)). A hearing will only be held if the Administrator determines that the material submitted shows the following: (1) There is a genuine and substantial issue of fact; (2) There is a reasonable probability that available evidence identified by the requestor would, if established, resolve one or more of such issues in favor of the requestor, taking into account uncontested claims to the contrary; and (3) Resolution of the issue(s) in the manner sought by the requestor would be adequate to justify the action requested (40 CFR 178.30).

You must file your objection or request a hearing on this regulation in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2021-0523 in the subject line on the first page of your submission. All requests must be in writing and must be received by the Hearing Clerk as required by 40 CFR part 178 on or before October 29, 2021.

II. Background

A. What action is the Agency taking?

EPA is revoking all tolerances for residues of chlorpyrifos. In 2007, the Pesticide Action Network North America (PANNA) and the Natural Resources Defense Council (NRDC) filed a petition with EPA under section 408(d) of the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. 346a(d), requesting that EPA revoke all

chlorpyrifos tolerances. (Ref. 1). In an April 29, 2021 decision concerning the Agency's orders denying that 2007 Petition and the subsequent objections to that denial, the Ninth Circuit ordered EPA to "(1) grant the 2007 Petition; (2) 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 from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information,' including for 'infants and children'; and (3) 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)." *League of United Latin Am. Citizens v. Regan*, 996 F.3d 673 (9th Cir. 2021) (the *LULAC* decision).

In today's action, EPA is granting the 2007 Petition, which requested revocation of the tolerances. While EPA previously responded to and denied the individual claims in the original petition, the Court found EPA's denial, at least with regard to the issues raised in the litigation, to be unsupported by the record before the Court and ordered EPA to grant the 2007 Petition and issue a final rule revoking or modifying tolerances. EPA is granting the petition by granting the relief sought by the petition, *i.e.*, the revocation of the chlorpyrifos tolerances, for the reasons stated in this rulemaking. Moreover, the Court expressly ordered EPA to respond to the petition by issuing a final rule under FFDCA section 408(d)(4)(A)(i). 996 F.3d at 702. That provision of the statute involves the issuance of a final rule "without further notice and without further period for public comment." 21 U.S.C. 346a(d)(4)(A)(i). While the FFDCA provides an option for EPA to respond to a petition with the issuance of a proposed rule under FFDCA section 408(d)(4)(A)(ii) and thereafter to finalize the proposal, the Court did not direct EPA to exercise its authority to finalize its 2015 proposal to revoke tolerances pursuant to subparagraph (d)(4)(A)(ii). Nothing in the Ninth Circuit's opinion reflects an expectation that, in complying with the Court's order, EPA would or should finalize the 2015 proposed rule. As such, EPA is viewing this action as independent from the 2015 proposal, and this final rule is based on the Agency's current assessment of the available scientific information, rather

than a continuation of and finalization of the Agency's proposal in 2015 to revoke chlorpyrifos tolerances.

In this final rule, EPA is revoking all tolerances for residues of chlorpyrifos contained in 40 CFR 180.342. This includes tolerances for residues of chlorpyrifos on specific food and feed commodities (180.342(a)(1)); on all food commodities treated in food handling and food service establishments in accordance with prescribed conditions (180.342(a)(2) and (a)(3)); and on specific commodities when used under regional registrations (180.342(c)).

EPA finds that, taking into consideration the currently available information and the currently registered uses of chlorpyrifos, EPA cannot make a safety finding to support leaving the current tolerances for residues of chlorpyrifos in place, as required under the FFDCFA section 408(b)(2). 21 U.S.C. 346a(b)(2). As described in greater detail below, the Agency's analysis indicates that aggregate exposures (*i.e.*, exposures from food, drinking water, and residential exposures), which stem from currently registered uses, exceed safe levels, when relying on the well-established 10% red blood cell acetylcholinesterase (RBC AChE) inhibition as an endpoint for risk assessment and including the statutory tenfold (10X) margin of safety to account for uncertainties related to the potential for neurodevelopmental effects to infants, children, and pregnant women. Accordingly, the Agency is therefore revoking all tolerances because given the currently registered uses of chlorpyrifos, EPA 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.

B. What is the Agency's authority for taking this action?

EPA is taking this action pursuant to the authority in FFDCFA sections 408(b)(1)(A), 408(b)(2)(A), and 408(d)(4)(A)(i). 21 U.S.C. 346a(b)(1)(A), (b)(2)(A), (d)(4)(A)(i).

C. Overview of Final Rule

When assessing pesticides, EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. For further discussion of the regulatory requirements of section 408 of the FFDCFA, see <https://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act>, and for a complete description of the risk assessment

process, see <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/overview-risk-assessment-pesticide-program> and <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/epas-risk-assessment-process-tolerance-reassessment>.

In general, to assess the risk of a pesticide tolerance, EPA combines information on pesticide toxicity with information regarding the route, magnitude, and duration of exposure to the pesticide. The risk assessment process involves four distinct steps: (1) Identification of the toxicological hazards posed by a pesticide; (2) Determination of the exposure "level of concern" for humans, which includes choosing a point of departure (PoD) that reflects the adverse health endpoint that is most sensitive to the pesticide, as well as uncertainty factors; (3) Estimation of human exposure to the pesticide through all applicable routes; and (4) Characterization of human risk based on comparison of the estimated human exposure to the level of concern. For tolerances, if aggregate exposure to humans is greater than the Agency's determined level of concern, the Agency's determination is the tolerances are not safe.

The following provides a brief roadmap of the Units in this rule.

- Unit III. contains an overview of the statutory background, including the safety standard in FFDCFA, and the registration standard under FIFRA. FFDCFA provides the statutory basis for evaluating tolerances and directs the Agency to revoke tolerances that are not safe.

- Unit IV. provides an overview of the FFDCFA petition that requested that EPA revoke chlorpyrifos tolerances on the grounds that those tolerances were not safe under the FFDCFA. While that petition raised numerous issues, the primary scientific challenge to the chlorpyrifos tolerances that was before the Ninth Circuit related to whether EPA had selected the correct PoD for assessing risk. While EPA's PoD was based on inhibition of the enzyme acetylcholinesterase (AChE), petitioners asserted that the most sensitive health endpoint was neurodevelopmental outcomes from exposure to chlorpyrifos. A summary of that petition, EPA's response to that petition, and the subsequent litigation and Ninth Circuit's order directing EPA to revoke or modify the chlorpyrifos tolerances is included in this section.

- Unit V. provides an overview of the regulatory background for chlorpyrifos, including the numerous human health risk assessments EPA has conducted

and FIFRA Scientific Advisory Panels (SAPs) that were convened to discuss the complex scientific issues associated with chlorpyrifos.

- Units VI. through VIII. summarizes EPA's risk assessment, which reflect the four-step process described above.

- Unit VI, which focuses on the hazard assessment of chlorpyrifos, combines the first two steps to provide a full picture of how EPA conducts its hazard assessment. After describing the process generally, this unit discusses EPA's analysis of the hazards posed by chlorpyrifos, including a discussion of the available data on AChE inhibition and the potential for neurodevelopmental outcomes in the young. Unit VI. also discusses the Agency's process for determining the endpoint on which to regulate chlorpyrifos exposure and the rationale for basing the PoD analysis on 10% AChE inhibition. Finally, this Unit includes a discussion of the FQPA safety factor and the Agency's reasons for retaining the default 10X value.

- Unit VII. describes EPA's exposure assessment for chlorpyrifos. The unit includes a description of the general approach for estimating exposures to pesticide residues in or on food and in drinking water, as well as exposures that come from non-occupational and non-dietary sources, also referred to as residential exposures. The unit walks through how EPA conducted those exposure assessments for chlorpyrifos, including a detailed discussion of the recent refinements to the drinking water analysis conducted by EPA for chlorpyrifos.

- Unit VIII. describes the Agency's process for assessing aggregate risk based on the hazard discussed in Unit VI. and the exposure discussed in Unit VII. and provides the Agency's rationale and conclusions concerning the overall risks posed by chlorpyrifos based on the currently registered uses. Unit VIII. concludes that the aggregate risks exceed the level of concern and therefore the chlorpyrifos tolerances must be revoked.

Units IX. and X. address procedural matters, international obligations, statutory and executive order review requirements, and the specific revisions that will be made to the Code of Federal Regulations with this final rule.

III. Statutory Background

A. Federal Food, Drug, and Cosmetic Act (FFDCFA) Tolerances

A "tolerance" represents the maximum level for residues of pesticide chemicals legally allowed in or on raw agricultural commodities and processed

foods. Section 408 of FFDCFA, 21 U.S.C. 346a, authorizes the establishment of tolerances, exemptions from tolerance requirements, modifications of tolerances, and revocation of tolerances for residues of pesticide chemicals in or on raw agricultural commodities and processed foods. Without a tolerance or exemption, pesticide residues in or on food is considered unsafe, 21 U.S.C. 346a(a)(1), and such food, which is then rendered “adulterated” under FFDCFA section 402(a), 21 U.S.C. 342(a), may not be distributed in interstate commerce, 21 U.S.C. 331(a).

Section 408(b)(2) of the FFDCFA directs that EPA may establish or leave in effect a tolerance for a pesticide only if it finds that the tolerance is safe, and EPA must revoke or modify tolerances determined to be unsafe. FFDCFA 408(b)(2)(A)(i) (21 U.S.C.

346a(b)(2)(A)(i)). Section 408(b)(2)(A)(ii) defines “safe” to mean that “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.” This includes exposure through food, drinking water and all non-occupational exposures (e.g., in residential settings), but does not include occupational exposures to workers (i.e., occupational). Risks to infants and children are given special consideration. Specifically, pursuant to section 408(b)(2)(C), EPA must assess the risk of the pesticide chemical based on available information concerning the special susceptibility of infants and children to the pesticide chemical residues, including neurological differences between infants and children and adults, and effects of in utero exposure to pesticide chemicals; and available information concerning the cumulative effects on infants and children of such residues and other substances that have a common mechanism of toxicity. (21 U.S.C. 346a(b)(2)(C)(i)(II) and (III)).

This provision further directs that “in the case of threshold effects, . . . an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of the data with respect to exposure and toxicity to infants and children.” (21 U.S.C. 346a(b)(2)(C)). EPA is permitted to “use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” (21 U.S.C. 346a(b)(2)(C)). Due to Congress’s focus on both pre- and postnatal toxicity, EPA

has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to prenatal exposure as well as to exposure during childhood years. This section providing for the special consideration of infants and children in section 408(b)(2)(C) was added to the FFDCFA through the Food Quality Protection Act (FQPA) (Pub. L. 104–170, 110 Stat. 1489 (1996)); therefore, this additional margin of safety is often referred to as the “FQPA safety factor (SF)”.

Section 408(d) of the FFDCFA, 21 U.S.C. 346a(d), authorizes EPA to revoke tolerances in response to an administrative petition submitted by any person. As explained in more detail in Unit IV, PANNA and NRDC submitted a petition in 2007 requesting revocation of all chlorpyrifos tolerances. The Ninth Circuit has directed EPA to grant that petition and issue a rule revoking or modifying those tolerances. EPA is issuing this rule in response to that petition and revoking all chlorpyrifos tolerances because EPA is unable to determine, based on data available at this time, that aggregate exposures to chlorpyrifos are safe.

B. Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Registration Review

Under FIFRA, a pesticide may not be sold or distributed in the United States unless it is registered. (7 U.S.C. 136a(a)). EPA must determine that a pesticide “will not generally cause unreasonable adverse effects on the environment in order to register a pesticide.” 7 U.S.C. 136a(c)(5). The term “unreasonable adverse effects on the environment” is defined to include “a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 346a of Title 21.” 7 U.S.C. 136(b). Thus, the FIFRA registration standard incorporates the FFDCFA safety standard and requires consideration of safety at the time of registration and during the registration review process.

Under section 3(g) of FIFRA (7 U.S.C. 136(a)(g)), EPA is required to re-evaluate existing registered pesticides every 15 years in a process called “registration review.” The purpose of registration review is “to ensure that each pesticide registration continues to satisfy the FIFRA standard for registration,” 40 CFR 155.40(a)(1), taking into account changes that have occurred since the last registration decision, including any new relevant scientific information and any changes to risk-assessment procedures, methods, and data requirements. 40 CFR 55.53(a). To ensure that a pesticide continues to

meet the standard for registration, EPA must determine, based on the available data, including any additional information that has become available since the pesticide was originally registered or re-evaluated, that the pesticide does not cause “unreasonable adverse effects on the environment.” 7 U.S.C. 136a(c)(1), (5); *see also* 40 CFR 152.50.

Chlorpyrifos is currently undergoing registration review, which must be completed by October 1, 2022. 7 U.S.C. 136a(g)(1)(A)(iv). For information about the ongoing registration review process for chlorpyrifos, see <https://www.regulations.gov/docket/EPA-HQ-OPP-2008-0850>.

IV. FFDCFA Petition and Related Litigation

A. 2007 FFDCFA Petition

In 2006, EPA issued the Registration Eligibility Decision (RED) for chlorpyrifos, which concluded that chlorpyrifos was eligible for reregistration as it continued to meet the FIFRA standard for registration. In September 2007, PANNA and NRDC submitted to EPA a petition (the Petition) seeking revocation of all chlorpyrifos tolerances under FFDCFA section 408 and cancellation of all chlorpyrifos pesticide product registrations under FIFRA. (Ref. 1). That petition raised several claims regarding EPA’s 2006 FIFRA reregistration decision for chlorpyrifos and the active registrations in support of the request for tolerance revocations and product cancellations. Those claims are described in detail in EPA’s earlier order denying the petition (82 FR 16581, April 5, 2017) (FRL–9960–77).

B. Agency Responses and 2017 Order Denying Petition

On March 29, 2017, EPA denied the Petition in full (82 FR 16581, April 5, 2017) (FRL–9960–77). Prior to issuing that order, EPA provided the Petitioners with two interim responses on July 16, 2012 and July 15, 2014, which denied six of the Petition’s claims. EPA made clear in both the 2012 and 2014 responses that, absent a request from Petitioners, EPA’s denial of those six claims would not be made final until EPA finalized its response to the entire Petition. Petitioners made no such request, and EPA therefore finalized its response to those claims in the March 29, 2017 Denial Order.

As background, three of the Petition’s claims all related to the same issue: Whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in children

at exposure levels below EPA's existing regulatory standard (10% RBC AChE inhibition). Because the claims relating to the potential for neurodevelopmental effects in children raised novel, highly complex scientific issues, EPA originally decided it would be appropriate to address these issues in connection with the registration review of chlorpyrifos under FIFRA section 3(g) and decided to expedite that review, intending to finalize it in 2015, well in advance of the October 1, 2022 registration review deadline (Ref. 2). EPA decided as a policy matter that it would address the Petition claims raising these matters on a similar timeframe. *Id.* at 16583.

The complexity of these scientific issues precluded EPA from finishing its review according to EPA's original timeline, and the Petitioners brought legal action in the Ninth Circuit Court of Appeals to compel EPA to either issue an order denying the Petition or to grant the Petition by initiating the tolerance revocation process. The result of that litigation was that on August 10, 2015, the Court ordered EPA to "issue either a proposed or final revocation rule or a full and final response to the administrative [P]etition by October 31, 2015." *In re Pesticide Action Network N. Am.*, 798 F.3d 809, 815 (9th Cir. 2015).

In response to that 2015 order, EPA issued a proposed rule to revoke all tolerances for chlorpyrifos on October 28, 2015 (published in the **Federal Register** on November 6, 2015 (80 FR 69080)), based on its unfinished registration review risk assessment. EPA acknowledged that it had had insufficient time to complete its drinking water assessment and its review of data addressing the potential for neurodevelopmental effects. Although EPA noted that further evaluation might enable more tailored risk mitigation, EPA was unable to conclude, based on the information before EPA at the time, that the tolerances were safe, since the aggregate exposure to chlorpyrifos exceeded safe levels.

On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to take final action on its proposed revocation rule and issue its final response to the Petition by December 30, 2016. *In re Pesticide Action Network N. Am.*, 808 F.3d 402 (9th Cir. 2015). In response to EPA's request for an extension of the deadline in order to be able to fully consider the July 2016 FIFRA Scientific Advisory Panel (SAP) report regarding chlorpyrifos toxicology, the Ninth Circuit ordered EPA to complete its final action by March 31, 2017. *In re Pesticide Action Network of*

North America v. EPA, 840 F.3d 1014 (9th Cir. 2016). Following that order, EPA published a Notice of Data Availability (NODA), seeking comment on EPA's revised risk assessment and water assessment and reopening the comment period on the proposal to revoke tolerances. (81 FR 81049, November 17, 2016) (FRL-9954-65).

On March 29, 2017, and as published in the **Federal Register** on April 5, 2017, the EPA issued an order denying the Petition (the Denial Order) (82 FR 16581). The specific responses are described in full in that Denial Order and summarized again in the Agency's denial of objections (84 FR 35555, July 24, 2019) (FRL-9997-06). EPA's Denial Order did not issue a determination concerning the safety of chlorpyrifos. Rather, EPA concluded that, despite several years of study, the science addressing neurodevelopmental effects remained unresolved and that further evaluation of the science on this issue during the remaining time for completion of registration review was warranted. EPA therefore denied the remaining Petition claims, concluding that it was not required to complete—and would not complete—the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without resolution of those issues during the ongoing FIFRA registration review of chlorpyrifos.

C. Objections and EPA's Denial of Objections

In June 2017, several public interest groups and states filed objections to the Denial Order pursuant to the procedures in FFDCA section 408(g)(2). Specifically, Earthjustice submitted objections on behalf of the following 12 public interest groups: Petitioners PANNA and NRDC, United Farm Workers, California Rural Legal Assistance Foundation, Farmworker Association of Florida, Farmworker Justice, GreenLatinos, Labor Council for Latin American Advancement, League of United Latin American Citizens, Learning Disabilities Association of America, National Hispanic Medical Association and Pineros y Campesinos Unidos del Noroeste. Another public interest group, the North Coast River Alliance, submitted separate objections. With respect to the states, New York, Washington, California, Massachusetts, Maine, Maryland, and Vermont submitted a joint set of objections (Ref. 1). The objections focused on three main topics: (1) The Objectors asserted that the FFDCA requires that EPA apply the FFDCA safety standard in reviewing any petition to revoke tolerances and that EPA's decision to deny the Petition

without making a safety finding failed to apply that standard; (2) The Objectors contended that the risk assessments EPA conducted in support of the 2015 proposed rule and the 2016 Revised Human Health Risk Assessment (HHRA) demonstrated that chlorpyrifos results in unsafe drinking water exposures and adverse neurodevelopmental effects and that EPA therefore was required to issue a final rule revoking all chlorpyrifos tolerances; and (3) The Objectors claimed that EPA committed procedural error in failing to respond to comments, and they specifically pointed to comments related to neurodevelopmental effects, inhalation risk, and Dow AgroSciences' (now doing business as Corteva AgriScience) physiologically based pharmacokinetic model (PBPK model) used in EPA's 2014 and 2015 human health risk assessments, which are discussed further in Unit V.

On July 18, 2019, EPA issued a final order denying all objections to the Denial Order and thereby completing EPA's administrative denial of the Petition (the Final Order) (84 FR 35555). Again, the Final Order did not issue a determination concerning the safety of chlorpyrifos. Rather, EPA denied the objections in part on the grounds that the data concerning neurodevelopmental toxicity were not sufficiently valid, complete, and reliable to meet the petitioners' burden.

D. Judicial Challenge to Objections Denial and 2021 Ninth Circuit Order

On August 7, 2019, the Objectors (LULAC Petitioners) and States petitioned the Ninth Circuit for review of the Denial Order and the Final Order. The LULAC Petitioners and States argued that EPA was compelled to grant the 2007 Petition and revoke chlorpyrifos tolerances because (1) EPA lacked authority to maintain chlorpyrifos tolerances without an affirmative finding that chlorpyrifos is safe, (2) EPA's findings that chlorpyrifos is unsafe in the Agency's risk assessments from 2014 and 2016, compel it to revoke chlorpyrifos tolerances, and (3) The 2007 Petition provided a sufficient basis for EPA to reconsider the question of chlorpyrifos's safety and was not required to prove that a pesticide is unsafe.

On April 29, 2021, the Ninth Circuit issued its decision, finding that when EPA denied the 2007 Petition to revoke chlorpyrifos tolerances, it was essentially leaving those chlorpyrifos tolerances in effect, which, the Court noted, the FFDCA only permits if EPA has made a determination that such tolerances were safe. *League of United*

Latin Am. Citizens v. Regan, 996 F.3d. 673 (9th Cir. 2021). Although EPA argued that it was not compelled to reconsider its safety determination because the 2007 Petition had failed to meet the threshold requirement of providing reliable evidence that the tolerances were unsafe, the Court found that the Petition provided the necessary “reasonable grounds,” which triggered EPA’s duty to ensure the tolerances were safe. *Id.* at 695. Since EPA’s Denial Order and Final Order failed to make any safety determinations for chlorpyrifos, the Court concluded that EPA violated the FFDCA by leaving those tolerances in place without the requisite safety findings. *Id.* at 695–96. Moreover, in light of the record before the Court, including the 2016 HHRA indicating that the current chlorpyrifos tolerances are not safe, the Court found EPA’s denial of the 2007 Petition to be arbitrary and capricious. *Id.* at 697. Based on the available record, the Court concluded that EPA must grant the Petition and issue a final rule modifying or revoking the tolerances under FFDCA section 408(d)(4)(A)(i). *Id.* at 701.

The Court recognized that EPA had been continuing to evaluate chlorpyrifos in registration review and had issued additional regulatory documents concerning chlorpyrifos after the record closed in the litigation, *e.g.*, the 2020 Proposed Interim Registration Review Decision and 2020 SAP, both of which are discussed in more detail in Unit V. below, and noted that such information could be relevant to a safety determination. *Id.* at 703. The Court allowed that if the new information could support a safety determination, EPA might issue a final rule modifying chlorpyrifos tolerances rather than revoking them, although the Court directed EPA to act “immediately” and not engage in “further factfinding.” *Id.* at 703. As a result, the Court ordered EPA to: (1) Grant the 2007 Petition; (2) Issue a final rule within 60 days of the issuance of the mandate that either revokes all chlorpyrifos tolerances or modifies chlorpyrifos tolerances, provided that such modification is supported by a safety finding, and (3) Modify or cancel related FIFRA registrations for food use in a timely fashion. *Id.* at 703–04. Since the mandate was issued on June 21, 2021, the deadline for issuing this final rule is August 20, 2021.

V. Chlorpyrifos Background and Regulatory History

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide.

Given the complex scientific nature of the issues reflected in this rule, EPA is alerting the reader that many of the technical terms used in this unit will be described more fully in a subsequent unit.

Chlorpyrifos, like other OP pesticides, affects the nervous system by inhibiting acetylcholinesterase (AChE), an enzyme necessary for the proper functioning of the nervous system. This can ultimately lead to signs of neurotoxicity. As discussed in more detail below, while there are data that indicate an association between chlorpyrifos and neurodevelopmental outcomes, there remains uncertainty in the dose-response relationship and the levels at which these outcomes occur. In an effort to resolve this scientific uncertainty, evaluation of toxicology and epidemiology studies of chlorpyrifos, specific to determining the appropriate regulatory endpoint, has been the focus of EPA’s work on chlorpyrifos for over a decade.

Chlorpyrifos has been registered for use in the United States since 1965. Currently registered use sites include a large variety of food crops (including fruit and nut trees, many types of fruits and vegetables, and grain crops), and non-food use settings (*e.g.*, golf course turf, industrial sites, greenhouse and nursery production, sod farms, and wood products). Public health uses include aerial and ground-based fogger mosquito adulticide treatments, roach bait products, and individual fire ant mound treatments. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments. *See, e.g.*, 65 FR 76233, December 6, 2000 (FRL–6758–2); 66 FR 47481, September 12, 2001 (FRL–6799–7).

In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides, concluding that the existing tolerances were safe and that chlorpyrifos continued to meet the FIFRA standard for registration. In that effort, EPA relied on RBC AChE inhibition as the endpoint for examining risk.

Subsequently, given ongoing scientific developments in the study of the OPs generally, EPA chose to prioritize the FIFRA section 3(g) registration review (the subsequent round of re-evaluation following reregistration) of chlorpyrifos and the OP class. The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific

issues which the Agency has taken to multiple independent FIFRA SAP reviews. (*Note:* The SAP is a federal advisory committee created by FIFRA section 25(d), 7 U.S.C. 136w(d), and serves as EPA’s primary source of peer review for significant regulatory and policy matters involving pesticides.)

These SAPs, which have included the review of new worker and non-occupational exposure methods, experimental toxicology and epidemiology, and the evaluation of a chlorpyrifos-specific physiologically-based pharmacokinetic-pharmacodynamic (PBPK–PD, see Unit VII. for definitions) model. These FIFRA SAP reviews have resulted in significant developments in EPA’s risk assessments generally, and, more specifically, in the study of chlorpyrifos’s effects. In particular, and partly in response to the issues raised in the 2007 Petition, EPA has conducted extensive reviews of available data to evaluate the possible connection between chlorpyrifos and adverse neurodevelopmental effects, and to assess whether the neurodevelopmental effects could be used to determine points of departure (PoDs) for assessing chlorpyrifos. On this particular topic, EPA has convened three FIFRA SAP reviews. EPA has taken FIFRA SAP recommendations into consideration as it has developed risk assessments and regulatory documents for chlorpyrifos. The remainder of this Unit provides a brief regulatory overview for chlorpyrifos by presenting a summary of the chronology of the FIFRA SAPs and Agency assessments of chlorpyrifos.

The 2008 FIFRA SAP evaluated the Agency’s preliminary review of available literature and research on epidemiology in mothers and children following exposures to chlorpyrifos and other OPs, laboratory studies on animal behavior and cognition, AChE inhibition, and mechanisms of action. (Ref. 3) The 2008 FIFRA SAP recommended that AChE inhibition remain as the source of data for the points of departure (PoDs, see Unit VII. for definitions), but noted that despite some uncertainties, the Columbia Center for Children’s Environmental Health (CCCEH) epidemiologic studies “is epidemiologically sound” and “provided extremely valuable information” for evaluating the potential neurodevelopmental effects of chlorpyrifos (Ref. 3). See Unit VI.A.2. for neurodevelopmental toxicity.

The 2010 FIFRA SAP favorably reviewed EPA’s 2010 draft epidemiology framework. (Ref. 4, 5) This draft framework, titled “Framework for Incorporating Human

Epidemiologic & Incident Data in Risk Assessments in Pesticides,” described the use of the Bradford Hill Criteria as modified in the Mode of Action Framework to integrate epidemiology information with other lines of evidence. As suggested by the 2010 FIFRA SAP, EPA did not immediately finalize the draft framework but instead used it in several pesticide evaluations prior to making revisions and finalizing it. EPA’s Office of Pesticide Program’s (OPP) finalized this epidemiology framework in December 2016 (Ref. 5).

In 2011, EPA released its preliminary human health risk assessment (2011 HHRA) for the registration review of chlorpyrifos. The 2011 HHRA used 10% RBC AChE inhibition from laboratory rats as the critical effect (or PoD) for extrapolating risk. It also used the default 10X uncertainty factors for inter- and intra-species extrapolation. The 10X FQPA SF was removed with a note to the public that a weight of evidence (WOE) evaluation would be forthcoming, as described in the 2010 draft “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment.”

In 2011, EPA convened a meeting of the FIFRA SAP to review the PBPK–PD model for chlorpyrifos. The panel made numerous recommendations for the improvement of the model for use in regulatory risk assessment, including the inclusion of dermal and inhalation routes. From 2011–2014, Dow AgroSciences, in consultation with EPA, refined the PBPK–PD model, and those refinements were sufficient to allow for use of the PBPK–PD model in the next HHRA.

In 2012, the Agency convened another meeting of the FIFRA SAP to review the latest experimental data related to RBC AChE inhibition, cholinergic and non-cholinergic adverse outcomes, including neurodevelopmental studies on behavior and cognition effects. The Agency also performed an in-depth analysis of the available chlorpyrifos biomonitoring data and of the available epidemiologic studies from three major children’s health cohort studies in the United States, including those from the CCCEH, Mount Sinai, and University of California, Berkeley. The Agency explored plausible hypotheses on mode of actions/adverse outcome pathways (MOAs/AOPs) leading to neurodevelopmental outcomes seen in the biomonitoring and epidemiology studies.

The 2012 FIFRA SAP described the Agency’s epidemiology review as “very clearly written, accurate” and “very thorough review”. (Ref. 6 at 50–52, 53) It went further to note that it “believes

that the [Agency’s] epidemiology review appropriately concludes that the studies show some consistent associations relating exposure measures to abnormal reflexes in the newborn, pervasive development disorder at 24 or 36 months, mental development at 7–9 years, and attention and behavior problems at 3 and 5 years of age. . . .” The 2012 FIFRA SAP concluded that the RBC AChE inhibition remained the most robust dose-response data, though expressed significant concerns about the degree to which 10% RBC AChE inhibition is protective for neurodevelopmental effects, pointing to evidence from epidemiology, *in vivo* animal studies, and *in vitro* mechanistic studies, and urged the EPA to find ways to use the CCCEH data.

In 2014, EPA released a revised human health risk assessment (2014 HHRA). (Ref. 7). The revised assessment used the chlorpyrifos PBPK–PD model for deriving human PoDs for RBC AChE inhibition, thus obviating the need for the inter-species extrapolation factor (as explained later in this Unit) and providing highly refined PoDs which accounted for gender, age, duration and route specific exposure considerations. The PBPK–PD model was also used to develop data derived intra-species factors for some lifestages. The 10X FQPA SF was retained based on the outcome of the 2012 FIFRA SAP and development of a WOE analysis on potential for neurodevelopmental outcomes according to EPA’s “Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides.” The 2014 HHRA, taken together with the Agency’s drinking water assessment, identified estimated aggregate risks exceeding the level of concern for chlorpyrifos.

On November 6, 2015, EPA issued a proposed rule to revoke all tolerances of chlorpyrifos, based on the aggregate risks exceeding the level of concern (80 FR 69079) (FRL–9935–92). In this proposed rulemaking, EPA specified that it was unable to conclude that aggregate exposures from use of chlorpyrifos met the FFDCA’s “reasonable certainty of no harm” standard due to risks identified from the drinking water using a national-scale assessment (*i.e.*, using default values and conservative assumptions). At that time, the EPA had not completed a refined drinking water assessment (*i.e.*, a higher-tier and more resource-intensive assessment relying on more targeted inputs) or an additional analysis of the hazard of chlorpyrifos that was suggested by several commenters to the 2014 HHRA. Those

commenters raised the concern that the use of 10% RBC AChE inhibition for deriving PoDs for chlorpyrifos may not provide a sufficiently health protective human health risk assessment given the potential for neurodevelopmental outcomes.

In 2015, EPA conducted additional hazard analyses using data on chlorpyrifos levels in fetal cord blood reported by the CCCEH study investigators. The Agency convened another meeting of the FIFRA SAP in April 2016 to evaluate a proposal of using cord blood data from the CCCEH epidemiology studies as the source of data for the PoDs. The 2016 SAP did not support the “direct use” of the cord blood and working memory data for deriving the regulatory endpoint, due in part to insufficient information about timing and magnitude of chlorpyrifos applications in relation to cord blood concentrations at the time of birth, uncertainties about the prenatal window(s) of exposure linked to reported effects, lack of a second laboratory to reproduce the analytical blood concentrations, and lack of raw data from the epidemiology study. (Ref. 8)

Despite its critiques of uncertainties in the CCCEH studies, the 2016 FIFRA SAP expressed concern that 10% RBC AChE inhibition is not sufficiently protective of human health. Specifically, the FIFRA SAP stated that it “agrees that both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% RBC AChE inhibition (*i.e.*, toxicity at lower doses).” (Id. at 18). (Ref. 8)

Taking into consideration the conclusions of the 2016 SAP, EPA issued another HHRA using a dose reconstruction approach to derive the PoD based on the neurodevelopmental effects observed in the CCCEH study. In 2016, EPA also issued a revised drinking water assessment (2016 DWA). EPA issued a Notice of Data Availability seeking public comment on the 2016 HHRA and 2016 DWA. (81 FR 81049, November 17, 2016) (FRL–9954–65).

In 2017, in response to a Ninth Circuit order, EPA denied the 2007 Petition on the grounds that “further evaluation of the science during the remaining time for completion of registration review is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos.” (82 FR at 16583). As part of this commitment to further evaluate the science, EPA evaluated the new laboratory animal studies with results

suggesting effects on the developing brain occur at doses lower than doses that cause AChE inhibition, and concluded that they are not sufficient for setting a PoD. While EPA sought to verify the conclusions of the epidemiology studies conducted by Columbia University it has been unable to confirm the findings of the CCCEH papers or conduct alternative statistical analyses to evaluate the findings. In summary, while EPA sought to address the potential neurodevelopmental effects associated with chlorpyrifos exposure over the past decade, these efforts ultimately concluded with the lack of a suitable regulatory endpoint based on these potential effects. However, these efforts do not alleviate the Agency's concerns regarding potential neurodevelopmental effects.

In October 2020, EPA released its latest human health risk assessment (2020 HHRA) and drinking water assessment (2020 DWA). (Ref. 9 and 10) Due to the shortcomings of the data upon which the 2016 HHRA was based and the uncertainty surrounding the levels around which neurodevelopmental effects may occur, the 2020 HHRA uses the same endpoint and PoDs as those used in the 2014 HHRA (*i.e.*, the PBPK-PD model has been used to estimate exposure levels resulting in 10% RBC AChE inhibition following acute (single day, 24 hours) and steady state (21-day) exposures for a variety of exposure scenarios for chlorpyrifos and/or chlorpyrifos oxon). The 2020 HHRA retained the default 10X FQPA SF, but also presented risk estimates at a reduced 1X FQPA SF, though it did not adopt or attempt to justify use of this approach.

Then, in December 2020, as part of its FIFRA registration review, EPA issued its Proposed Interim Registration Review Decision (2020 PID) for chlorpyrifos (85 FR 78849, December 7, 2020) (FRL-10017-13). The 2020 PID was based on comparing estimates in the 2020 HHRA with the values from the 2020 DWA, and retaining the 10X FQPA safety factor, the PID proposed to limit applications of chlorpyrifos in this country would be reduced to certain uses in certain regions of the United States. The PID proposed to conclude that the Agency could make a safety finding for the approach in this path forward, as risk would be based on limited uses in limited geographic areas, as specified. This proposed path forward was intended to offer to stakeholders a way to mitigate the aggregate risk from chlorpyrifos, which the Agency had determined would exceed risk levels of concern without the proposed use restrictions.

In December 2020, EPA requested public comment on the 2020 PID, 2020 HHRA, and 2020 DWA. EPA extended the 60-day comment period by 30 days and it closed on March 7, 2021.

VI. EPA's Hazard Assessment for Chlorpyrifos

A. General Approach to Hazard Identification, Dose-Response Assessment, and Extrapolation

Any risk assessment begins with an evaluation of a chemical's inherent properties, and whether those properties have the potential to cause adverse effects (*i.e.*, a hazard identification). In evaluating toxicity or hazard, EPA reviews toxicity data, typically from studies with laboratory animals, to identify any adverse effects on the test subjects. Where available and appropriate, EPA will also take into account studies involving humans, including human epidemiological studies. The animal toxicity database for a conventional, food use pesticide usually consists of studies investigating a broad range of endpoints including potential for carcinogenicity, mutagenicity, developmental and reproductive toxicity, and neurotoxicity. These studies include gross and microscopic effects on organs and tissues, functional effects on bodily organs and systems, effects on blood parameters (such as red blood cell count, hemoglobin concentration, hematocrit, and a measure of clotting potential), effects on the concentrations of normal blood chemicals (including glucose, total cholesterol, urea nitrogen, creatinine, total protein, total bilirubin, albumin, hormones, and enzymes such as alkaline phosphatase, alanine aminotransferase and cholinesterases), and behavioral or other gross effects identified through clinical observation and measurement. EPA examines whether adverse effects are caused by different durations of exposure ranging from short-term (acute) to long-term (chronic) pesticide exposure and different routes of exposure (oral, dermal, inhalation). Further, EPA evaluates potential adverse effects in different age groups (adults as well as fetuses and juveniles). (Ref. 11 at 8-10).

Once a pesticide's potential hazards are identified, EPA determines a toxicological level of concern for evaluating the risk posed by human exposure to the pesticide. In this step of the risk assessment process, EPA essentially evaluates the levels of exposure to the pesticide at which effects might occur. An important aspect of this determination is assessing the relationship between exposure (dose)

and response (often referred to as the dose-response analysis). In evaluating a chemical's dietary risks, EPA uses a reference dose (RfD) approach, which typically involves a number of considerations including:

- A "point of departure" (PoD): Typically, the PoD is the value from a dose-response curve that is at the low end of the observable data in laboratory animals and that is the toxic dose that serves as the 'starting point' in extrapolating a risk to the human population, although a PoD can also be derived from human data as well. PoDs are selected to be protective of the most sensitive adverse toxic effect for each exposure scenario, and are chosen from toxicity studies that show clearly defined No Observed Adverse Effect Levels (NOAELs) or Lowest Observed Adverse Effect Levels (LOAELs), dose-response relationships, and relationships between the chemical exposure and effect. EPA will select separate PoDs, as needed, for each expected exposure duration (*e.g.*, acute, chronic, short-term, intermediate-term) and route of exposure (*e.g.*, oral, dermal, inhalation). For chlorpyrifos, as discussed later in this Unit, EPA derived PoDs based on 10% RBC AChE inhibition.

- *Interspecies extrapolation*: Because most PoDs are derived from toxicology studies in laboratory animals, there is a need to extrapolate from animals to humans. In typical risk assessments, a default tenfold (10X) uncertainty factor is used to address the potential for a difference in toxic response between humans and animals used in toxicity tests. For chlorpyrifos, as described further below, EPA used a sophisticated model called a physiologically based pharmacokinetic-pharmacodynamic (PBPK-PD) model that accounts for differences in laboratory animals and humans, thereby obviating the need for the default interspecies factor.

- *Intraspecies extrapolation*: To address the potential for differences in sensitivity in the toxic response across the human population, EPA conducts intraspecies extrapolation. In typical risk assessments, a 10X default uncertainty factor is used. For chlorpyrifos, the PBPK-PD model used to derive PoDs also accounts for differences in metabolism and toxicity response across the human population for some age groups and some subpopulations, which allows the default factor of 10X to be refined in accordance with EPA's 2014 *Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation*.

• *Food Quality Protection Act safety factor (FQPA SF)*: The FFDCA section 408(b)(2)(C) instructs EPA, in making its “reasonable certainty of no harm” finding, that in “the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and post-natal toxicity and completeness of data with respect to exposure and toxicity to infants and children.” Section 408(b)(2)(C) further states that “the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of reliable data, such margin will be safe for infants and children.” For chlorpyrifos, as discussed later in this Unit, EPA is retaining the default 10X FQPA SF.

In the human health risk assessment process, as indicated above, EPA uses the selected PoD to calculate a RfD for extrapolating risk. The RfD is calculated by dividing the selected PoD by any applicable interspecies and intraspecies factors and other relevant uncertainty factors such as LOAEL to NOAEL factor or database uncertainty factor.

After calculating the RfD, as indicated above, EPA retains an additional safety factor of 10X to protect infants and children (the FQPA safety factor), unless reliable data support selection of a different factor, as required under the FFDCA. As described in EPA’s policy for determining the appropriate FQPA safety factor, this additional safety factor often overlaps with other traditional uncertainty factors (e.g., LOAEL to NOAEL factor or database uncertainty factor), but it might also account for residual concerns related to pre- and postnatal toxicity or exposure. (Ref. 35 at 13–16) In implementing FFDCA section 408, EPA calculates a variant of the RfD referred to as a Population Adjusted Dose (PAD), by dividing the RfD by the FQPA SF. Risk estimates less than 100% of the PAD are safe.

B. Toxicological Effects of Chlorpyrifos

Consistent with FFDCA section 408(b)(2)(D), EPA has reviewed the available scientific data and other relevant information for chlorpyrifos in support of this action. For over a decade, EPA has evaluated the scientific evidence surrounding the different health effects associated with chlorpyrifos. The Agency has conducted extensive reviews of the scientific literature on health outcomes associated with chlorpyrifos and presented approaches for evaluating and using that information to the FIFRA SAP on several occasions, as discussed above in

Unit V. Chlorpyrifos has been tested in toxicological studies for the potential to cause numerous different adverse outcomes (e.g., reproductive toxicity, developmental toxicity, cancer, genotoxicity, dermal toxicity, endocrine toxicity, inhalation toxicity, and immunotoxicity). The inhibition of AChE leading to cholinergic neurotoxicity and the potential for effects on the developing brain (i.e., neurodevelopmental effects) are the most sensitive effects seen in the available data. (2020 HHRA p. 6). The SAP reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the data in conducting EPA’s registration review human health risk assessment for chlorpyrifos.

Unit VI. discusses the Agency’s assessment of the science relating to AChE inhibition and the potential for neurodevelopmental effects. Other adverse outcomes besides AChE inhibition and neurodevelopment are less sensitive and are thus not discussed in detail here. Further information concerning those effects can be found in the 2000 human health risk assessment which supported the RED and the 2011 preliminary human health risk assessment. (Ref. 12 and 13).

1. Acetylcholinesterase (AChE) Inhibition

Chlorpyrifos, like other OP pesticides, affects the nervous system by inhibiting AChE, an enzyme necessary for the proper functioning of the nervous system and ultimately leading to signs of neurotoxicity. This mode of action, in which AChE inhibition leads to neurotoxicity, is well-established, and thus has been used as basis for the PoD for OP human health risk assessments, including chlorpyrifos. This science policy is based on decades of work, which shows that AChE inhibition is the initial event in the pathway to acute cholinergic neurotoxicity.

The Agency has conducted a comprehensive review of the available data and public literature regarding this adverse effect from chlorpyrifos. (Ref. 8 at 24–25, Ref. 13 at 25–27) There are many chlorpyrifos studies evaluating RBC AChE inhibition or the brain in multiple lifestages (gestational, fetal, post-natal, and non-pregnant adult), multiple species (rat, mouse, rabbit, dog, human), methods of oral administration (oral gavage with corn oil, dietary, gavage via milk) and routes of exposure (oral, dermal, inhalation via vapor and via aerosol). In addition, chlorpyrifos is unique in the availability of AChE data from peripheral tissues in some studies

(e.g., heart, lung, liver). There are also literature studies comparing the *in vitro* AChE response to a variety of tissues which show similar sensitivity and intrinsic activity. Across the database, brain AChE tends to be less sensitive than RBC AChE or peripheral AChE. In oral studies, RBC AChE inhibition is generally similar in response to peripheral tissues. Thus, the *in vitro* data and oral studies combined support the continued use of RBC AChE inhibition as the critical effect for quantitative dose-response assessment.

Female rats tend to be more sensitive than males to these AChE effects. For chlorpyrifos, there are data from multiple studies which provide robust RBC AChE data in pregnant, lactating, and non-pregnant female rats from oral exposure (e.g., developmental neurotoxicity (DNT), reproductive, and subchronic data).

In addition, studies are available in juvenile pups which show age-dependent differences, particularly following acute exposures, in sensitivity to chlorpyrifos and its oxon. As discussed above, this sensitivity is not derived from differences in the AChE enzyme itself but instead are derived largely from the immature metabolic clearance capacity in the juveniles.

2. Neurodevelopmental Toxicity

In addition to information on the effects of chlorpyrifos on AChE, there is an extensive body of information (in the form of laboratory animal studies, epidemiological studies, and mechanistic studies) studying the potential effects on neurodevelopment in infants and children following exposure to OPs, including chlorpyrifos.

There are numerous laboratory animal studies on chlorpyrifos in the literature that have evaluated the impact of chlorpyrifos exposure in pre- and post-natal dosing on the developing brain. These studies vary substantially in their study design, but all involve gestational and/or early postnatal dosing with behavioral evaluation from adolescence to adulthood. The data provide qualitative support for chlorpyrifos to potentially impact the developing mammalian brain with adverse outcomes in several neurological domains including cognitive, anxiety and emotion, social interactions, and neuromotor function. It is, however, important to note that there is little consistency in patterns of effects across studies. In addition, most of these studies use doses that far exceed EPA’s 10% benchmark response level for RBC AChE inhibition. There are only a few studies with doses at or near the 10% brain or RBC AChE inhibition levels;

among these only studies from Carr laboratory at Mississippi State University are considered by EPA to be high quality. EPA has concluded that the laboratory animal studies on neurodevelopmental outcomes are not sufficient for quantitatively establishing a PoD. Moreover, EPA has further concluded that the laboratory animal studies do not support a conclusion that adverse neurodevelopmental outcomes are more sensitive than 10% RBC AChE inhibition. (Ref. 8 at 25–31, Ref. 9 at 88–89).

EPA evaluated numerous epidemiological studies on chlorpyrifos and other OP pesticides in accordance with the “Framework for Incorporating Human Epidemiologic & Incident Data in Health Risk Assessment.” (Ref. 8, 14, and 15) The most robust epidemiologic research comes from three prospective birth cohort studies. These include: (1) The Mothers and Newborn Study of North Manhattan and South Bronx performed by the Columbia Children’s Center for Environmental Health (CCCEH) at Columbia University; (2) the Mount Sinai Inner-City Toxicants, Child Growth and Development Study or the “Mt. Sinai Child Growth and Development Study;” and (3) the Center for Health Assessment of Mothers and Children of Salinas Valley (CHAMACOS) conducted by researchers at University of California Berkeley. (Ref. 8 at 32–43).

In the case of the CCCEH study, which specifically evaluated the possible connections between chlorpyrifos levels in cord blood and neurodevelopmental outcomes on a specific cohort, there are a number of notable associations. (Ref. 8 at 36–38). Regarding infant and toddler neurodevelopment, the CCCEH authors reported statistically significant deficits of 6.5 points on the Psychomotor Development Index at three years of age when comparing high to low exposure groups. Notably, these decrements persist even after adjustment for group and individual level socioeconomic variables. These investigators also observed increased odds of mental delay and psychomotor delay at age three when comparing high to low exposure groups. The CCCEH authors also report strong, consistent evidence of a positive association for attention disorders, attention deficit hyperactivity disorder (ADHD), and pervasive development disorder (PDD) when comparing high to low chlorpyrifos exposure groups. Moreover, it was reported that for children in the CCCEH cohort at age seven for each standard deviation increase in chlorpyrifos cord blood exposure, there is a 1.4% reduction in

Full-Scale IQ and a 2.8% reduction in Working Memory. In addition, the CCCEH authors evaluated the relationship between prenatal chlorpyrifos exposure and motor development/movement and reported elevated risks of arm tremor in children around 11 years of age in the CCCEH cohort.

Notwithstanding the observed associations, EPA and the 2012 and 2016 FIFRA SAPs identified multiple uncertainties in the CCCEH epidemiology studies (Ref. 6 and 8). Some of these include the relatively modest sample sizes, which limited the statistical power; exposure at one point in prenatal time with no additional information regarding postnatal exposures; representativeness of a single point exposure where time-varying exposures or the ability to define cumulative exposures would be preferable; lack of specificity of a critical window of effect and the potential for misclassification of individual exposure measures; and lack of availability of the raw data from the studies that would allow verification of study conclusions.

One of the notable uncertainties in the CCCEH epidemiology studies identified by EPA and the 2016 FIFRA SAP is the lack of specific exposure information on the timing, frequency, and magnitude of chlorpyrifos application(s) in the apartments of the women in the study. Despite extensive effort by EPA to obtain or infer this exposure information from various sources, the lack of specific exposure data remains a critical uncertainty. EPA made efforts in 2014 and 2016 to develop dose reconstruction of the exposures to these women. These dose reconstruction activities represent the best available information and tools but are highly uncertain. In addition, the pregnant women and children in the CCCEH studies were exposed to multiple chemicals, including multiple potent AChE inhibiting OPs and *N*-methyl carbamates. Moreover, using EPA’s dose reconstruction methods from 2014 suggest that the pregnant women likely did not exhibit RBC AChE inhibition above 10%. The 2012 and 2016 FIFRA SAP reports expressed concern that it is likely that the CCCEH findings occurred at exposure levels below those that result in 10% RBC AChE inhibition (Ref. 6 and 8). However, given the available CCCEH exposure information and the exposures to multiple potent AChE inhibiting pesticides, EPA cannot definitively conclude the level of AChE inhibition. EPA remains unable to make a causal linkage between chlorpyrifos exposure and the outcomes reported by

CCCEH investigators. (Ref. 8) Moreover, given the uncertainties, particularly in the exposure information available from CCCEH (single timepoints, lack of time varying exposure, lack of knowledge about application timing), uncertainties remain about the dose-response relationships from the epidemiology studies.

Finally, there are several lines of evidence for actions of chlorpyrifos distinct from the classical mode of action of AChE inhibition. This information has been generated from model systems representing different levels of biological organization and provide support for molecular initiating events (binding to the morphogenic site of AChE, muscarinic receptors, or tubulin), cellular responses (alterations in neuronal proliferation, differentiation, neurite growth, or intracellular signaling), and responses at the level of the intact nervous system (serotonergic tone, axonal transport). Among the many *in vitro* studies on endpoints relevant to the developing brain available for chlorpyrifos, only three have identified outcomes in picomole concentrations, including concentrations lower than those that elicit AChE inhibition *in vitro*. However, as is the case for many other developmental neurotoxicants, most of these studies have not been designed with the specific goal of construction or testing an adverse outcome pathway. Thus, there are not sufficient data available to test rigorously the causal relationship between effects of chlorpyrifos at the different levels of biological organization in the nervous system. (Ref. 8 at 27–31)

Due to the complexity of nervous system development involving the interplay of many different cell types and developmental timelines, it is generally accepted that no single *in vitro* screening assay can recapitulate all the critical processes of neurodevelopment. As a result, there has been an international effort to develop a battery of new approach methodologies (NAMs) to inform the DNT potential for individual chemicals. This DNT NAM battery is comprised of *in vitro* assays that assess critical processes of neurodevelopment, including neural network formation and function, cell proliferation, apoptosis, neurite outgrowth, synaptogenesis, migration, and differentiation. In combination the assays in this battery provide a mechanistic understanding of the underlying biological processes that may be vulnerable to chemically-induced disruption. It is noteworthy, however, that to date the quantitative relationship between alterations in these

neurodevelopmental processes and adverse health outcomes has not been fully elucidated. Moreover, additional assays evaluating other critical neurodevelopmental processes such as myelination are still being developed (Ref. 15).

In September 2020, EPA convened a FIFRA SAP on developing and implementing NAMs using methods such as *in vitro* techniques and computational approaches. Included in that consideration was use of the DNT NAM battery to evaluate OP compounds as a case study. These methods presented to the 2020 FIFRA SAP provide a more systematic approach to evaluating pharmacodynamic effects on the developing brain compared to the existing literature studies. Initial data from the NAM battery were presented to the SAP for 27 OP compounds, including chlorpyrifos and its metabolite, chlorpyrifos oxon, and, when possible, compared to *in vivo* results (by using *in vitro* to *in vivo* extrapolation). On December 21, 2020, the SAP released its final report and recommendations on EPA's proposed use of the NAMs data. (Ref. 16). The advice of the SAP is currently being taken into consideration as EPA develops a path forward on NAMs, but analysis and implementation of NAMs for risk assessment of chlorpyrifos is in progress and was unable to be completed in time for use in this rulemaking. The Agency is continuing to explore the use of NAMs for the OPs, including chlorpyrifos, and intends to make its findings available as soon as it completes this work.

C. Hazard Identification: Using AChE as the Toxicological Endpoint for Deriving PADs

The RED for chlorpyrifos was completed in 2006 and relied on RBC AChE inhibition results from laboratory animals to derive PoDs and retained the FQPA 10X safety factor due to concerns over age-related sensitivity and uncertainty associated with potential neurodevelopmental effects observed in laboratory animals. Based on a review of all the studies (guideline data required, peer reviewed literature, mechanistic), AChE inhibition remains the most robust quantitative dose-response data and thus continues to be the critical effect for the quantitative risk assessment. This approach is consistent with the advice of the SAP from 2008 and 2012. The Agency typically uses a 10% response level for AChE inhibition in human health risk assessments. This response level is consistent with the 2006 OP cumulative risk assessment

and other single chemical OP risk assessments. (Ref. 17 and 18).

In response to the 2015 proposed rule to revoke chlorpyrifos tolerances, as noted above, the Agency received some comments raising a concern that the use of the 10% AChE inhibition may not be sufficiently health protective. Taking those comments into consideration, EPA conducted an additional hazard analysis and convened the 2016 FIFRA SAP to evaluate a proposal of using cord blood data from the CCCEH epidemiology studies as the source of data for PoDs. The 2016 FIFRA SAP did not support the "direct use" of the cord blood and working memory data for deriving the regulatory endpoint, due to insufficient information about timing and magnitude of chlorpyrifos applications in relation to cord blood concentrations at the time of birth, uncertainties about the prenatal window(s) of exposure linked to reported effects, and lack of a second laboratory to reproduce the analytical blood concentrations. (Ref. 8) Despite their critiques regarding uncertainties in the CCCEH studies, the 2016 SAP expressed concern that 10% RBC AChE inhibition is not sufficiently protective of human health.

The 2016 FIFRA SAP, however, did present an alternative approach for EPA to consider. First, it is important to note that this SAP was supportive of the EPA's use of the PBPK-PD model as a tool for assessing internal dosimetry from typical OPP exposure scenarios. Use of the PBPK-PD model coupled with typical exposure scenarios provides the strongest scientific foundation for chlorpyrifos human health risk assessment. Given that the window(s) of susceptibility are currently not known for the observed neurodevelopmental effects, and the uncertainties associated with quantitatively interpreting the CCCEH cord blood data, this SAP recommended that the Agency use a time weighted average (TWA) blood concentration of chlorpyrifos for the CCCEH study cohort as the PoD for risk assessment. Thus, in 2016 EPA attempted, using the PBPK-PD model, to determine the TWA blood level expected from post-application exposures from the chlorpyrifos indoor crack-and-crevice use scenario. Despite that effort, EPA's position is that the shortcomings of the data with regard to the dose-response relationship and lack of exposure information discussed above, continue to raise issues that make quantitative use of the CCCEH data in risk assessment not scientifically sound.

Thus, taking into consideration the robustness of the available data at this time, EPA has determined that the most

appropriate toxicological endpoint for deriving points of departure for assessing risks of chlorpyrifos is 10% RBC AChE inhibition. The Agency is not ignoring or dismissing the extensive data concerning the potential for adverse neurodevelopmental outcomes, however. As discussed later in this Unit, the Agency is addressing the uncertainties surrounding the potential for adverse neurodevelopmental outcomes by retaining the default 10X FQPA safety factor.

1. Durations of Exposure

As noted in Unit VI.A., EPA establishes PoDs for each expected exposure duration likely to result from pesticide exposure. For chlorpyrifos, exposure can occur from a single event or on a single day (*e.g.*, eating a meal) or from repeated days of exposure (*e.g.*, residential). With respect to AChE inhibition, effects can occur from a single exposure or from repeated exposures. For OPs, repeated exposures generally result in more AChE inhibition at a given administered dose compared to acute exposures. Moreover, AChE inhibition in repeated dosing guideline toxicology studies with most OPs show a consistent pattern of inhibition reaching a "steady state" of inhibition at or around 2–3 weeks of exposure in adult laboratory animals (Ref. 19). This pattern observed with repeated dosing is a result of the amount of inhibition coming to equilibrium with production of new enzyme. As such, AChE studies of 2–3 weeks generally show the same degree of inhibition with those of longer duration (*i.e.*, up to 2 years of exposure). Thus, for most of the human health risk assessments for the OPs, the Agency is focusing on the critical durations ranging from a single day up to 21 days (*i.e.*, the approximate time to reach steady state for most OPs). As such, EPA has calculated PoDs for the acute and steady-state durations. As described below, these PoDs have been derived for various lifestages, routes, and exposure scenarios.

2. Deriving PODs, Inter- and Intra-Species Extrapolation: Use of the PBPK Model

The process for developing RfDs and PADs typically involves first deriving PoDs directly from laboratory animal studies, followed by dividing the PoD by the default uncertainty factors of 10X for interspecies extrapolation and intraspecies extrapolation, and the FQPA safety factor. For chlorpyrifos, as discussed previously in Unit V, there is a sophisticated PBPK-PD model available for chlorpyrifos. Numerous

Federal Advisory Committees and external review panels have encouraged the use of such a modeling approach to reduce inherent uncertainty in the risk assessment and facilitate more scientifically sound extrapolations across studies, species, routes, and dose levels. The PBPK–PD model for chlorpyrifos has undergone extensive peer review by various individual or groups, including the FIFRA SAPs. Significant improvements have been made to the model over the years in response to recommendations from the 2008, 2011, and 2012 FIFRA SAPs and comments from both internal and external peer reviewers. (Ref. 9 at 20). As a result, EPA has concluded that the current PBPK–PD model is sufficiently robust and is using it for deriving PoDs for chlorpyrifos.

a. Derivation of PoDs

As noted above, the PoDs for chlorpyrifos are based on the levels at which 10% RBC AChE inhibition is observed. The PBPK–PD model accounts for pharmacokinetic and pharmacodynamic characteristics to derive age-, duration-, and route-specific PoDs. Separate PoDs have been calculated for dietary (food, drinking water) and residential exposures by varying inputs on types of exposures and populations exposed. Specifically, the following characteristics have been evaluated: Duration [24-hour (acute), 21-day (steady state)]; route (dermal, oral, inhalation); body weights which vary by lifestage; exposure duration (hours per day, days per week); and exposure frequency [events per day (eating, drinking)]. For each exposure scenario, the appropriate body weight for each age group or sex was modeled as identified from the Exposure Factors Handbook (Ref. 21) for residential exposures and from the U.S. Department of Agriculture's (USDA) National Health and Nutrition Examination Survey (NHANES)/What We Eat in America (WWEIA) Survey for dietary exposures.

Within the PBPK–PD model, the Agency evaluated the following exposure scenarios: Oxon (chlorpyrifos metabolite) exposures via drinking water (acute and steady-state exposures for infants, children, youths, and female adults); chlorpyrifos exposures via food (acute and steady-state exposures for infants, children, youths, and female adults); steady-state residential exposures to chlorpyrifos via skin for children, youths, and female adults; steady-state residential exposures to chlorpyrifos via hand-to-mouth ingestion for children 1–2 years old; steady-state residential exposures to chlorpyrifos via inhalation for children

1–2 years old and female adults. (Ref. 9 at 22–25).

Steady-state dietary exposure was estimated daily for 21 days. For drinking water exposure, infants and young childrens (infants <1 year old, children between 1–2 years old, and children between 6–12 years old) were assumed to consume water 6 times per day, with a total consumption volume of 0.69 L/day. For youths and female adults, they were assumed to consume water 4 times per day, with a total consumption volume of 1.71 L/day.

For all residential dermal exposures to chlorpyrifos the dermal PoDs were estimated assuming 50% of the skin's surface was exposed. Exposure times for dermal exposure assessment were consistent with those recommended in the 2012 Residential Standard Operating Procedures (SOPs) (Ref. 18). For residential inhalation exposures following public health mosquitoicide application, the exposure duration was set to 1 hour per day for 21 days. The incidental oral PoDs for children 1 to <2 years old for other turf activities were estimated assuming that there were six events, 15 minutes apart, per day.

The PBPK-modeled PoDs derived for the various lifestages, routes, and exposure scenarios discussed above, can be found in Table 4.2.2.1.2 of the 2020 HHRA (Ref 8).

b. Inter-Species Extrapolation

As indicated above, the PBPK–PD model directly predicts human PoDs based on human physiology and biochemistry, and thus there is no need for an inter-species uncertainty factor to extrapolate from animal PoDs.

c. Intra-Species Extrapolation

The PBPK–PD model can account for variability of critical physiological, pharmacokinetic, and pharmacodynamic parameters in a population to estimate, using the Monte Carlo analysis, the distribution of doses that result in 10% RBC AChE inhibition. Therefore, Data-Derived Extrapolation Factors (DDEF) for intra-species extrapolation have been estimated to replace the default intra-species uncertainty factor for some groups (Ref. 22).

According to EPA's DDEF guidance (Ref. 22), when calculating a DDEF intra-species extrapolation factor, administered doses leading to the response level of interest (in the case of chlorpyrifos, the 10% change in RBC AChE inhibition) are compared between a measure of average response and response at the tail of the distribution representing sensitive individuals. The

tail of the distribution may be selected at the 95th, 97.5th, and 99th percentile.

As to chlorpyrifos, the 99th percentile was used in risk assessment to provide the most conservative measure (Ref. 7). In addition to estimating DDEF using the above approach for specific age groups, intra-species DDEF was also calculated by comparing between average responses between adults and 6-month old infants. For the 2020 HHRA, the largest calculated DDEFs, 4X for chlorpyrifos and 5X for the oxon metabolite, were used for intraspecies extrapolation for all groups except women of childbearing age. There was a slightly higher variability between adults and infants when considering the distributions for the oxon metabolite, thus, the slightly higher intra-species factor. For women of childbearing age, the Agency is applying the standard 10X intra-species extrapolation factor due to limitations in the PBPK–PD model to account for physiological, anatomical, and biochemical changes associated with pregnancy. (Ref. 9 at 21–22).

d. Summarizing the PoDs, Inter- and Intra-Species Extrapolation Factors

In summary, for assessing the risks from exposure to chlorpyrifos, the human PBPK–PD model has been used to derive PoDs based on 10% RBC AChE inhibition for various populations, durations, and routes. The model, which calculates a human PoD directly, obviates the need for an interspecies extrapolation factor since animal data are not used. To account for variations in sensitivities, the Agency has determined that an intra-species factor of 4X for chlorpyrifos and 5X for the oxon is appropriate for all groups except women of childbearing age. For women of childbearing age, the typical 10X intra-species factor is being applied, due the lack of appropriate information and algorithms to characterize physiological changes during pregnancy.

3. FQPA Safety Factor

As noted above, the FFDCA requires EPA, in making its "reasonable certainty of no harm" finding, that in "the case of threshold effects, an additional tenfold margin of safety for the pesticide chemical residue and other sources of exposure shall be applied for infants and children to take into account potential pre- and postnatal toxicity and completeness of data with respect to exposure and toxicity to infants and children." 21 U.S.C. 346A(b)(2)(C). Section 408(b)(2)(C) further states that "the Administrator may use a different margin of safety for the pesticide chemical residue only if, on the basis of

reliable data, such margin will be safe for infants and children.”

In applying the FQPA safety factor provision, EPA has interpreted it as imposing a presumption in favor of retaining it as an additional 10X safety factor. (Ref. 5 at 4, 11). Thus, EPA generally refers to the 10X factor as a presumptive or default 10X factor. EPA has also made clear, however, that this presumption or default in favor of the 10X is only a presumption. The presumption can be overcome if reliable data demonstrate that a different factor is safe for children. (Id.). In determining whether a different factor is safe for children, EPA focuses on the three factors listed in FFDC section 408(b)(2)(C)—the completeness of the toxicity database, the completeness of the exposure database, and potential pre- and post-natal toxicity. In examining these factors, EPA strives to make sure that its choice of a safety factor, based on a weight-of-the-evidence evaluation, does not understate the risk to children. (Id. at 24–25, 35).

EPA’s 2020 HHRA assessed the potential risks from exposures to chlorpyrifos in two ways—with one scenario being the retention of the default 10X FQPA SF, and the other scenario being the reduction of the FQPA SF to 1X. The purpose of using both values was to provide an indication of what the potential risk estimates would be under either scenario. The 2020 document, however, retained the 10X and did not adopt or offer support for reducing to 1X. To reduce the FQPA safety factor to 1X, the FFDC requires that EPA determine that reliable data demonstrate that the 1X would be safe for infants and children. The 2020 document did not make that determination. For chlorpyrifos, of the three factors mentioned in the previous paragraph, the primary factor that undercuts a determination that a different safety factor would be safe for children is the uncertainty around the potential for pre- and post-natal toxicity for infants and children in the area of neurodevelopmental outcomes.

Based on the weight of the evidence concerning the potential for neurodevelopmental outcomes as discussed in Unit VI.B.2. above, there is ample qualitative evidence of a potential effect on the developing brain; however, there remains uncertainty around the levels at which these potential neurodevelopmental outcomes occur. Although the laboratory animal studies do not support a conclusion that neurodevelopmental outcomes are more sensitive than AChE inhibition, the

mechanistic data are, at this time, incomplete in their characterization of dose-response. This conclusion may be further evaluated upon EPA’s completion of the review of the 2020 FIFRA SAP report concerning NAMs; however, due to the time constraints of this rule, EPA has not been able to include that information in the current assessment of chlorpyrifos. Finally, while the epidemiology data indicates an association between chlorpyrifos and adverse neurodevelopmental outcomes, there remains some uncertainty in the dose-response relationship. As such, because the data available at this time indicate remaining uncertainties concerning pre- and post-natal toxicity due to insufficient clarity on the levels at which these outcomes occur, the Agency is unable to conclude, at this time, that a different safety factor would be safe for infants and children; thus, the Agency is retaining the default 10X FQPA safety factor.

4. Total Uncertainty Factors and PADs

In conclusion, the Agency used a total uncertainty factor of 100X for determining the food and drinking water PADs for females of childbearing age (1X interspecies factor, 10X intra-species factor, and 10X FQPA safety factor); 40X for determining the food PADs for remaining populations (1X interspecies factor, 4X intra-species factor, and 10X FQPA safety factor); and 50X for determining the PADs for drinking water for remaining populations (1X interspecies factor, 5X intra-species factor, and 10X FQPA safety factor).

Taking into consideration the PoDs, intra-species extrapolation factors, and FQPA safety factor, the Agency calculated acute PADs (aPADs) and steady state PADs (ssPADs) for infants (less than 1 year old), children (1 to 2 years old), children (6 to 12 years old), youths (13 to 19 years old), and females (13–49 years old); these subpopulations will be protective of other subpopulations. (Ref. 9 at 30–32.) Values may be found in table 5.0.1 in the 2020 HHRA.

VII. EPA’s Exposure Assessment for Chlorpyrifos

Risk is a function of both hazard and exposure. Thus, equally important to the risk assessment process as determining the hazards posed by a pesticide and the toxicological endpoints for those hazards is estimating human exposure. Under FFDC section 408, EPA must evaluate the aggregate exposure to a pesticide chemical residue. This means that EPA is concerned not only with exposure to

pesticide residues in food but also exposure resulting from pesticide contamination of drinking water supplies and from use of pesticides in the home or other non-occupational settings. (See 21 U.S.C. 346a(b)(2)(D)(vi)).

Pursuant to FFDC section 408(b), EPA has evaluated chlorpyrifos’s risks based on “aggregate exposure” to chlorpyrifos. By “aggregate exposure,” EPA is referring to exposure to chlorpyrifos by multiple pathways of exposure, *i.e.*, food, drinking water, and residential. EPA uses available data and standard analytical methods, together with assumptions designed to be protective of public health, to produce separate estimates of exposure for a highly exposed subgroup of the general population, for each potential pathway and route of exposure.

The following reflect a summary of the Agency’s exposure assessment from the 2020 HHRA unless otherwise specified. (Ref. 10).

A. Exposure From Food

1. General Approach for Estimating Food Exposures

There are two critical variables in estimating exposure in food: (1) The types and amount of food that is consumed; and (2) The residue level in that food. Consumption is estimated by EPA based on scientific surveys of individuals’ food consumption in the United States conducted by the U.S. Department of Agriculture (USDA), (Ref. 11 at 12). Information on residue values can come from a range of sources including crop field trials; data on pesticide reduction (or concentration) due to processing, cooking, and other practices; information on the extent of usage of the pesticide; and monitoring of the food supply. (Id. at 17).

Data on the residues of chlorpyrifos in foods are available from both field trial data and monitoring data, primarily the USDA’s Pesticide Data Program (PDP) monitoring data. Monitoring data generally provide a characterization of pesticide residues in or on foods consumed by the U.S. population that closely approximates real world exposures because they are sampled closer to the point of consumption in the chain of commerce than field trial data, which are generated to establish the maximum level of legal residues that could result from maximum permissible use of the pesticide immediately after harvest.

EPA uses a computer program known as the Dietary Exposure Evaluation Model and Calendex software with the Food Commodity Intake Database

(DEEM–FCID version 3.16/Calendex) to estimate exposure by combining data on human consumption amounts with residue values in food commodities. The model incorporates 2003–2008 consumption data from USDA’s NHANES/WWEIA. The data are based on the reported consumption of more than 20,000 individuals over two non-consecutive survey days. Foods “as consumed” (e.g., apple pie) are linked to EPA-defined food commodities (e.g., apples, peeled fruit—cooked; fresh or N/S (Not Specified); baked; or wheat flour—cooked; fresh or N/S, baked) using publicly available recipe translation files developed jointly by USDA Agricultural Research Service (ARS) and EPA. For chronic exposure assessment (or in the case of chlorpyrifos, for steady-state exposure assessment), consumption data are averaged for the entire U.S. population and within population subgroups; however, for acute exposure assessment, consumption data are retained as individual consumption events. Using this consumption information and residue data, the exposure estimates are calculated for the general U.S. population and specific subgroups based on age, sex, ethnicity, and region.

For chlorpyrifos, EPA determined that acute and steady-state exposure durations were relevant for assessing risk from food consumption. EPA calculates potential risk by using probabilistic techniques to combine distributions of potential exposures in sentinel populations. The resulting probabilistic assessments present a range of dietary exposure/risk estimates.

Because probabilistic assessments generally present a realistic range of residue values to which the population may be exposed, EPA’s starting point for estimating exposure and risk for such assessments is the 99.9th percentile of the population under evaluation. When using a probabilistic method of estimating acute dietary exposure, EPA typically assumes that, when the 99.9th percentile of acute exposure is equal to or less than the aPAD, the level of concern for acute risk has not been exceeded. By contrast, where the analysis indicates that estimated exposure at the 99.9th percentile exceeds the aPAD, EPA would generally conduct one or more sensitivity analyses to determine the extent to which the estimated exposures at the high-end percentiles may be affected by unusually high food consumption or residue values. (The same assumptions apply to estimates for steady state dietary exposure and the ssPAD.) To the extent that one or a few values seem to “drive” the exposure estimates at the

high-end of exposure, EPA would consider whether these values are reasonable and should be used as the primary basis for regulatory decision making (Ref. 20).

2. Estimating Chlorpyrifos Exposures in Food

The residue of concern, for tolerance expression and risk assessment, in plants (food and feed) and livestock commodities is the parent compound chlorpyrifos. EPA has determined that the metabolite chlorpyrifos oxon is not a residue of concern in food or feed, based on available field trial data and metabolism studies that indicate that the oxon is not present in the edible portions of the crops. In addition, the chlorpyrifos oxon is not found on samples in the USDA PDP monitoring data. Furthermore, the oxon metabolite was not found in milk or livestock tissues (Ref. 9 at 33).

Acute and steady-state dietary (food only) exposure analyses for chlorpyrifos were conducted using the DEEM–FCID version 3.16/Calendex software (Ref. 23). These analyses were performed for the purpose of obtaining food exposure values for comparison to the chlorpyrifos doses predicted by the PBPK–PD model to cause RBC AChE Inhibition. The acute and steady-state dietary (food only) exposure analyses do not include drinking water exposures, which were assessed separately, see Unit VII.B.2.

Both the acute and steady state dietary exposure analyses are highly refined. The large majority of food residues used were based upon PDP monitoring data except in a few instances where no appropriate PDP data were available. In those cases, field trial data or tolerance level residues were assumed. EPA also used food processing factors from submitted studies as appropriate. In addition, EPA’s acute and steady state dietary exposure assessments used percent crop treated (PCT) information. (Ref. 23)

The chlorpyrifos acute dietary exposure analysis was conducted using the DEEM–FCID, version 3.16, which incorporates 2003–2008 survey consumption data from USDA’s NHANES/WWEIA. The acute risk estimates were presented for the sentinel populations for infants (less than 1 yr old); children (1–2 years old); youths (6–12 years old); and adults (females 13–49 years old). The assessment of these index lifestages is protective of other population subgroups.

The chlorpyrifos steady-state dietary exposure analysis was conducted using the Calendex component of DEEM–FCID

(with 2003–2008 survey consumption data from USDA’s NHANES/WWEIA). Calendex provides a focus detailed profile of potential exposures to individuals across a calendar year. A calendar-based approach provides the ability to estimate daily exposures from multiple sources over time to an individual and is in keeping with two key tenets of aggregate risk assessment: (1) That exposures when aggregated are internally consistent and realistic; and (2) that appropriate temporal and geographic linkages or correlations/associations between exposure scenarios are maintained.

The chlorpyrifos steady state assessment considers the potential risk from a 21-day exposure duration using a 3-week rolling average (sliding by day) across the year. For this assessment, the same food residue values used in the acute assessment were used for the 21-day duration. In the Calendex software, one diary for each individual in the WWEIA is selected to be paired with a randomly selected set of residue values for each food consumed. The steady-state analysis calculated exposures for the sentinel populations for infants (less than 1 year old); children (1–2 years old); youths (6–12 years old); and adults (females 13–49 years old). The assessment of these index lifestages is protective of other population subgroups.

B. Exposure From Drinking Water

1. General Approach for Assessing Exposure From Drinking Water

a. Modeling and Monitoring Data

Monitoring and modeling are both important tools for estimating pesticide concentrations in water and can provide different types of information. Monitoring data can provide estimates of pesticide concentrations in water that are representative of the specific agricultural or residential pesticide practices in specific locations, under the environmental conditions associated with a sampling design (i.e., the locations of sampling, the times of the year samples were taken, and the frequency by which samples were collected). Although monitoring data can provide a direct measure of the concentration of a pesticide in water, it does not always provide a reliable basis for estimating spatial and temporal variability in exposures because sampling may not occur in areas with the highest pesticide use, and/or when the pesticides are being used and/or at an appropriate sampling frequency to detect high concentrations of a pesticide that occur over the period of a day to several days.

Because of the limitations in most monitoring studies, EPA's standard approach is to use water exposure models as the primary means to estimate pesticide exposure levels in drinking water. Modeling is a useful tool for characterizing vulnerable sites and can be used to estimate upper-end pesticide water concentrations from infrequent, large rain events. EPA's computer models use detailed information on soil properties, crop characteristics, and weather patterns to estimate water concentrations in vulnerable locations where the pesticide could be used according to its label (Ref. 24 at 27–28). EPA's models calculate estimated water concentrations of pesticides using laboratory data that describe how fast the pesticide breaks down to other chemicals and how it moves in the environment at these vulnerable locations. The modeling provides an estimate of pesticide concentrations in ground water and surface water. Depending on the modeling algorithm (e.g., surface water modeling scenarios), daily concentrations can be estimated continuously over long periods of time, and for places that are of most interest for any particular pesticide.

EPA relies on models it has developed for estimating pesticide concentrations in both surface water and groundwater. The most common model used to conduct drinking water assessments is the Pesticide in Water Calculator (PWC). PWC couples the Pesticide Root Zone Model (PRZM) and Variable Volume Water Model (VVWM) models together to simulate pesticide fate and transport from the field of application to an adjacent reservoir. (Ref. 24 at 27–28). The PWC estimates pesticide concentrations for an index reservoir that is modeled for site-specific scenarios (i.e., weather and soil data) in different areas of the country. A detailed description of the models routinely used for exposure assessment is available from the EPA OPP Aquatic Models website: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/models-pesticide-risk-assessment#aquatic>.

In modeling potential surface water concentrations, EPA attempts to model areas of the country that are vulnerable to surface water contamination rather than simply model "typical" concentrations occurring across the nation. Consequently, EPA models exposures occurring in small highly agricultural watersheds in different growing areas throughout the country, over a 30-year period. The scenarios are designed to capture residue levels in drinking water from reservoirs with

small watersheds with a large percentage of land use in agricultural production. EPA believes these assessments are likely reflective of a small subset of the watersheds across the country that maintain drinking water reservoirs, representing a drinking water source generally considered to be more vulnerable to frequent high concentrations of pesticides than most locations that could be used for crop production.

When monitoring data meet certain data quantity criteria, EPA has tools available to quantify the uncertainty in available monitoring data such that it can be used quantitatively to estimate pesticide concentrations in drinking water. (Ref. 25) Furthermore, monitoring data can be used in a weight of evidence approach with model estimated concentrations to increase confidence in the conclusions of a drinking water assessment.

b. Drinking Water Level of Comparison (DWLOC)

The drinking water level of comparison (DWLOC) is a benchmark that can be used to guide refinements of the drinking water assessment (DWA). This value relates to the concept of the "risk cup," which EPA developed to facilitate risk refinement when considering aggregate human health risk to a pesticide. (Ref. 26). The risk cup is the total exposure allowed for a pesticide considering its toxicity and required safety factors. The risk cup is equal to the maximum safe exposure for the duration and population being considered. Exposures exceeding the risk cup are of potential concern. There are risk cups for each pertinent duration of exposure (e.g., acute, short-term, chronic). The exposure durations most commonly of interest for acute or short-term pesticide exposure risk assessments are 1-day, 4-day, and 21-day averages. For example, the relevant exposure duration for AChE reversible inhibition from exposure to carbamate insecticides is 1-day, while AChE irreversible inhibition resulting from exposure to OP insecticides is usually 21-days based on steady-state kinetics. (Ref. 19)

In practice, EPA calculates the total exposure from food consumption and residential (or other non-occupational) exposures and subtracts this value from the maximum safe exposure level. The resulting value is the allowable remaining exposure without the potential for adverse health effect. Knowing this allowable remaining exposure and the water consumption for each population subgroup (e.g., infants), the Agency can calculate the DWLOC,

which is the estimate of safe concentrations of pesticides in drinking water. Using this process of DWLOC calculation allows EPA to determine a target maximum safe drinking water concentration, thereby identifying instances where drinking water estimates require refinement. (Ref. 24 at 19–20).

c. Scale of Drinking Water Assessment

Although food is distributed nationally, and residue values are therefore not expected to vary substantially throughout the country, drinking water is locally derived and concentrations of pesticides in source water fluctuate over time and location for a variety of reasons. Pesticide residues in water fluctuate daily, seasonally, and yearly because of the timing of the pesticide application, the vulnerability of the water supply to pesticide loading through runoff, spray drift and/or leaching, and changes in the weather. Concentrations are also affected by the method of application, the location, and characteristics of the sites where a pesticide is used, the climate, and the type and degree of pest pressure, which influences the application timing, rate used, and number of treatments in a crop production cycle.

EPA may conduct a drinking water assessment (DWA) for a national scale depending on the pesticide use under evaluation. A national scale DWA may use a single upper-end pesticide concentration as a starting point for assessing whether additional refinements are needed or estimated pesticide concentrations for certain site-specific scenarios that are associated with locations in the United States vulnerable to pesticide contamination based on pesticide use patterns. (Ref. 24 at 22.)

EPA may also conduct a regional scale DWA to focus on areas where pesticide concentrations may be higher than the DWLOC. Under this assessment, EPA estimates pesticide concentrations across different regions in the United States that are subdivided into different areas called hydrologic units (HUCs). There are 21 HUC 2 regions with 18 in the contiguous United States. These areas contain either the drainage area of a major river or a combined drainage of a series of rivers. This information can be found at: <https://water.usgs.gov/GIS/huc.html>. Estimated pesticide concentrations under this approach would be associated with a vulnerable pesticide use area somewhere within the evaluated region. (Ref. 24 at 23).

d. Drinking Water Refinements

EPA has defined four assessment tiers for drinking water assessments. Lower tiered assessments are more conservative based on the defaults or upper bound assumptions and may compound conservatisms, while higher tiers integrate more available data and provide more realistic estimates of environmental pesticide concentrations.

These four tiers are generally based on the level of effort, the amount of data considered, the spatial scale, and the certainty in the estimated pesticide concentration. Tier 1 requires the least amount of effort and the least amount of data, whereas Tier 4 is resource intensive, considers a wide range of sources and types of data, and is spatially explicit, resulting in high confidence in the reported pesticide concentration. Each successive tier integrates more focused pesticide, spatial, temporal, agronomic, and crop-specific information. The order in which refinements are considered (*i.e.*, the order in which the assessment is refined) is pesticide-specific and depends on the nature and quality of the available data used to support the refinement. Additional information on the conduct of drinking water assessments can be found in the “Framework for Conducting Pesticide Drinking Water Assessment for Surface Water” (USEPA, 2020).

As discussed in the Framework document, EPA can incorporate several refinements in higher tiered modeling. Two such refinements are the percent cropped area (PCA) and the percent crop treated (PCT). These are described in the recently completed document titled “*Integrating a Distributional Approach to Using Percent Crop Area (PCA) and Percent Crop Treated (PCT) into Drinking Water Assessment*” (Ref. 27) The PCA refers to the amount of area in a particular community water system that is planted with the crop of interest (*e.g.*, the default assumption is that the entire watershed is planted with a crop of interest). The PCT refers to the amount of the cropped area that is treated with the pesticide of interest (*e.g.*, the default is that the entire cropped area is treated with the pesticide of interest). With additional use and usage data, EPA can refine assumptions about the application rate and PCT for use in modeling to generate estimated drinking water concentrations (EDWCs) that are appropriate for human health risk assessment and more accurately account for the contribution from individual use patterns in the estimation of drinking water concentrations.

2. Drinking Water Assessment for Chlorpyrifos.

For the chlorpyrifos drinking water assessment, the metabolite chlorpyrifos oxon, which forms because of drinking water treatment and is more toxic than chlorpyrifos, was chosen as the residue of concern. (Ref. 28 and 29) The range of conversion from parent to oxon depends upon the type of water treatment and other conditions. Based on available information regarding the potential effects of certain water treatments (*e.g.*, chlorination appears to hasten transformation of chlorpyrifos to chlorpyrifos oxon), EPA assumed that all chlorpyrifos in source water is converted to chlorpyrifos oxon upon treatment.

The Agency used a DWLOC approach for assessing aggregate risk from chlorpyrifos. As such, EPA calculated DWLOCs for different age groups for both the acute aggregate assessment and the steady-state aggregate assessment, taking into consideration the food and residential contributions to the risk cup. These numbers were provided as a benchmark for evaluating drinking water contributions from uses of chlorpyrifos across the United States, and whether such concentrations would result in aggregate exposures to chlorpyrifos that exceeded the Agency’s levels of concern. The lowest acute DWLOC calculated was for exposure to chlorpyrifos oxon to infants (<1 year old) at 23 ppb; the lowest steady state DWLOC calculated was also for exposure to chlorpyrifos oxon to infants (<1 year old) at 4.0 ppb. (Ref. 9 at 45–45). In other words, EDWCs of chlorpyrifos oxon greater than 4.0 ppb for a 21-day average would exceed EPA’s DWLOC and present a risk that exceeds the Agency’s level of concern.

In its 2014 drinking water assessment, EPA concluded that there were multiple uses of chlorpyrifos that could lead to exposures to chlorpyrifos oxon in drinking water that exceed the DWLOC identified at that time. (Ref. 29). This assessment provided the basis for the Agency’s proposal to revoke tolerances in 2015. (Ref. 30). In 2016, EPA conducted a refined drinking water assessment that estimated drinking water concentrations based on modeling of all registered uses, as well as all available surface water monitoring data. That assessment considered several refinement strategies in a two-step process to derive exposure estimates for chlorpyrifos and chlorpyrifos oxon across the country. The first step was an assessment of potential exposure based on the current maximum label rates at

a national level. This indicated that the EDWCs could be above the DWLOC.

Because estimated concentrations at the national level exceeded the DWLOC, the Agency conducted a more refined assessment of uses on a regional level. (Ref. 28 at 73–86). This more refined analysis derived EDWCs using the PWC modeling for maximum labeled rates and 1 pound per acre by region for each use. The analysis indicated that approved uses of chlorpyrifos in certain vulnerable watersheds in every region of the country would result in EDWCs that exceed the DWLOC. For example, Table 25 of EPA’s 2016 DWA, which provides the range of estimated concentrations of chlorpyrifos in drinking water from uses on golf courses and agricultural or production crops, shows EDWCs that exceed the DWLOC in vulnerable watersheds in every region in the country. While the lower end of some of the ranges provided in that table are below the DWLOC, those lower numbers reflect a single use (*i.e.*, single crop) and do not reflect potential exposure from other uses where applications occur at higher rates, more frequently, or in more locations made more vulnerable due to soil type, weather, or agronomic practices. The relevant estimated concentration for risk assessment purposes is the highest concentration across all uses because it reflects concentrations that may occur in vulnerable sources of drinking water (Ref. 28 at 73–74).

In addition, a robust quantitative analysis of the monitoring data was conducted resulting in concentrations consistent with model-estimated concentrations above the DWLOC. (Ref. 28 at 90–121). Considering both monitoring data and modeling estimates together supports the conclusion that drinking water concentrations in regions across the country will exceed the DWLOC. (Ref. 28 at 121–123).

After the EPA’s 2016 DWA showed that the DWLOC exceedances are possible from several uses, EPA developed refinement strategies to examine those estimated regional/watershed drinking water concentrations to pinpoint community drinking water systems where exposure to chlorpyrifos oxon as a result of chlorpyrifos applications may pose an exposure concern. At that time, EPA was anticipating that a more refined drinking water assessment might allow EPA to better identify where at-risk watersheds are located throughout the country to support more targeted risk mitigation through the registration review process. The refinements better account for variability in the use area treated within a watershed that may

contribute to a drinking water intake (referred to as PCA or percent use area when considering non-agricultural uses) and incorporate data on the amount of a pesticide that is actually applied within a watershed for agricultural and non-agricultural uses (referred to as PCT). These refinement approaches underwent external peer review and were issued for public comment in January 2020: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/about-water-exposure-models-used-pesticide>. In addition, EPA used average application rates, average numbers of annual applications for specific crops, and estimated typical application timing at the state-level based on pesticide usage data derived from a statistically reliable private market survey database, publicly available survey data collected by the USDA, and state-specific scientific literature from crop extension experts.

The recently developed refinements were integrated in the *Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review*, which was issued in September 2020. (2020 DWA) (Ref. 10) The updated assessment applied the new methods for considering the entire distribution of community water systems PCA adjustment factors, integrated state level PCT data, incorporated refined usage and application data, and included quantitative use of surface water monitoring data in addition to considering state level usage rate and data information. In addition, given the 2016 DWA calculation of estimated drinking water concentrations exceeding the DWLOC of 4.0 ppb, the Agency decided to focus its refinements for the 2020 updated drinking water assessment on a subset of uses in specific regions of the United States. The purpose of the focus on this subset of uses was to determine, if these were the only uses permitted on the label, whether or not the resulting estimated drinking water concentrations would be below the DWLOC. The subset of uses assessed were selected because they were identified as critical uses by the registrant and/or high-benefit uses to growers. That subset of currently registered uses included alfalfa, apple, asparagus, cherry, citrus, cotton, peach, soybean, sugar beet, strawberry, and wheat in specific areas of the country. The results of this analysis indicated that the EDWCs from this subset of uses limited to certain regions are below the DWLOC. (Ref. 10 at 16–17). However, the 2020 DWA refined estimates did not include chlorpyrifos exposures from uses beyond that subset. In the 2020

DWA, EPA stated that if additional uses were added or additional geographic areas included, a new separate assessment would need to be prepared in order to evaluate whether concentrations would remain below the DWLOC. In addition to the modeling of the EDWCs for the specific subset of uses, the 2020 DWA conducted a quantitative surface water monitoring data analysis. That analysis indicated that monitored chlorpyrifos concentrations, which reflect existing uses, are above the DWLOC. (Ref. 10 at 62, 75). These data would need to be considered in the context of any additional uses beyond the subset evaluated.

C. Residential Exposure to Pesticides

1. General Approach to Assessing Non-Occupational Exposures

Residential assessments examine exposure to pesticides in non-occupational or residential settings (e.g., homes, parks, schools, athletic fields or any other areas frequented by the general public), based on registered uses of the pesticide. Exposures to pesticides may occur to persons who apply pesticides (which is referred to as residential handler exposure) or to persons who enter areas previously treated with pesticides (which is referred to as post-application exposure). Such exposures may occur through oral, inhalation, or dermal routes and may occur over different exposure durations (e.g., short-term, intermediate-term, long-term), depending on the type of pesticide and particular use pattern.

Residential assessments are conducted through examination of significant exposure scenarios (e.g., children playing on treated lawns or homeowners spraying their gardens) using a combination of generic and pesticide-specific data. To regularize this process, EPA has prepared SOPs for conducting residential assessments on a wide array of scenarios that are intended to address all major possible means by which individuals could be exposed to pesticides in a non-occupational environment (e.g., homes, schools, parks, athletic fields, or other publicly accessible locations). (Ref. 18) The SOPs identify relevant generic data and construct algorithms for calculating exposure amounts using these generic data in combination with pesticide-specific information. The generic data generally involve survey data on behavior patterns (e.g., activities conducted on turf and time spent on these activities) and transfer coefficient data. Transfer coefficient data measure

the amount of pesticide that transfers from the environment to humans from a defined activity (e.g., hand contact with a treated surface or plant). Specific information on pesticides can include information on residue levels as well as information on environmental fate such as degradation data.

Once EPA assesses all the potential exposures from all applicable exposure scenarios, EPA selects the highest exposure scenario for each exposed population to calculate representative risk estimates for use in the aggregate exposure assessment. Those specific exposure values are then combined with the life stage appropriate exposure values provided for food and drinking water to determine whether a safety finding can be made.

2. Residential Exposure Assessment for Chlorpyrifos

Most chlorpyrifos products registered for residential treatment were voluntarily cancelled or phased out by the registrants between 1997 and 2001; however, some uses of chlorpyrifos remain that may result in non-occupational, non-dietary (i.e., residential) exposures. Based on the remaining registered uses, the Agency has determined that residential handler exposures are unlikely. Chlorpyrifos products currently registered for residential use are limited to roach bait products or ant mound treatments. Exposures from the application of roach bait products are expected to be negligible. The roach bait product is designed such that the active ingredient is contained within a bait station, which eliminates the potential for contact with the chlorpyrifos containing bait material. Since the ant mound treatments can only be applied professionally, residential handler exposure is also not anticipated. (Ref. 9 at 36–44).

There is a potential for residential post-application exposures. Chlorpyrifos is registered for use on golf courses and as an aerial and ground-based ultra-low volume (ULV) mosquito adulticide applications made directly in residential areas. Based on the anticipated use patterns reviewed under the SOP, EPA assessed these exposures as steady-state residential post-application exposures, which would be protective of shorter durations of exposure. There is a potential for dermal post-application exposures from the golf course uses for adults (females 13–49 years old); youths (11 to less than 16 years old); and children (6 to less than 11 years old). There is also a potential for dermal, incidental oral, and inhalation post-application exposures

for children (1 to less than 2 years old) and dermal and inhalation post-application exposures for adults from exposure to mosquitoicide uses. The Agency combined post-application exposures for children (1 to less than 2 years old) for dermal, inhalation, and incidental oral exposure routes because these routes all share a common toxicological endpoint. EPA used the post-application exposures and risk estimates resulting from the golfing scenarios in its aggregate exposure and risk assessment.

VIII. Aggregate Risk Assessment and Conclusions Regarding Safety for Chlorpyrifos

The final step in the risk assessment is the aggregate exposure assessment and risk characterization. In this step, EPA combines information from the first three steps (hazard identification, level of concern (LOC)/dose-response analysis, and human exposure assessment) to quantitatively estimate the risks posed by a pesticide. The aggregated exposure assessment process considers exposure through multiple pathways or routes of exposure (*e.g.*, food, water, and residential) for different sub-populations (*e.g.*, infants, children ages 1–6) and exposure duration or types of effects (*e.g.*, acute noncancer effects (single dose), chronic noncancer effects, and cancer). The aggregated exposure assessments can be deterministic (levels of exposure for each pathway are point estimates), probabilistic (levels of exposure are a distribution for a given population), or a combination of the two and are dependent on the level of refinement or assessment tier.

As noted above, EPA evaluates aggregate exposure by comparing combined exposure from all relevant sources to the safe level. Where exposures exceed the safe level, those levels exceed the risk cup and are of potential concern. There are risk cups for each pertinent duration of exposure for a pesticide because the amount of exposure that can be incurred without adverse health effects will vary by duration (*e.g.*, acute, short-term, chronic). The risk cup is equal to the PAD (either acute, chronic, or steady-state), or the maximum safe exposure for short- and intermediate-term durations.

Whether risks will exceed the risk cup (*i.e.*, whether exposures are expected to exceed safe levels) is expressed differently, depending on the type of level of concern the Agency has identified. For dietary assessments, the risk is expressed as a percentage of the acceptable dose (*i.e.*, the dose which EPA has concluded will be “safe”).

Dietary exposures greater than 100% of the percentage of the acceptable dose are generally cause for concern and would be considered “unsafe” within the meaning of FFDCA section 408(b)(2)(B). For non-dietary (and combined dietary and non-dietary) risk assessments of threshold effects, the toxicological level of concern is typically not expressed as an RfD/PAD, but rather in terms of an acceptable (or target) Margin of Exposure (MOE) between human exposure and the PoD. The “margin” that is being referred to in the term MOE is the ratio between the PoD and human exposure which is calculated by dividing human exposure into the PoD. An acceptable MOE is generally considered to be a margin at least as high as the product of all applicable safety factors for a pesticide. For example, when the Agency retains the default uncertainty factors for dietary or aggregate risk (a 10X interspecies uncertainty factor, a 10X intraspecies uncertainty factor, and a 10X FQPA safety factor), the total uncertainty factors (or level of concern) is 1000, and any MOE above 1000 represents exposures that are not of concern. Like RfD/PADs, specific target MOEs are selected for exposures of different durations and routes. For non-dietary exposures, EPA typically examines short-term, intermediate-term, and long-term exposures. Additionally, target MOEs may be selected based on both the duration of exposure and the various routes of non-dietary exposure—dermal, inhalation, and oral. Target MOEs for a given pesticide can vary depending on the characteristics of the studies relied upon in choosing the PoD for the various duration and route scenarios.

In addition, in a DWLOC aggregate risk assessment, the calculated DWLOC is compared to the EDWC. Where EPA has calculated a DWLOC, EPA can determine whether drinking water exposures will result in aggregate risks of concern by comparing estimated pesticide concentrations in drinking water to the DWLOC. As noted above, an aggregate DWLOC represents the amount of allowable safe residues of pesticide in drinking water because it represents the room remaining in the risk cup after accounting for the food and residential exposures. The DWLOC provides an estimate of the allowable safe concentrations of pesticides in drinking water for comparison to EDWCs. When the EDWC is less than the DWLOC, there are no risk concerns for aggregate exposures because the Agency can conclude that the contribution from drinking water when

aggregated with food and non-occupational exposures will not exceed safe levels of exposure. Conversely, an EDWC at or exceeding the DWLOC would indicate a risk of concern, as those exposures to chlorpyrifos in drinking water, when aggregated with exposures from food and residential exposures, would exceed safe levels of exposure. (Ref. 31).

A. Dietary Risks From Food Exposures

As noted above, EPA’s acute and steady state dietary exposures assessments for chlorpyrifos were highly refined and incorporated monitoring data for almost all foods. The Agency assessed food exposures based on approved registered uses of chlorpyrifos. This includes field uses of chlorpyrifos but not potential exposure from food handling establishment uses since the Agency did not identify any registered food handling establishment uses. (Ref. 9 at 33–36).

Considering food exposures alone, the Agency did not identify risks of concern for either acute or steady state exposures. Acute dietary (food only) risk estimates, which are based on risk from a single exposure event in the 2020 HHRA were all below 100 percent of the acute population adjusted dose for food (aPAD_{food}) at the 99.9th percentile of exposure and are not of concern. The population with the highest risk estimate was females (13–49 years old) at 3.2% aPAD_{food}. Steady-state dietary (food only) risk estimates, which are based on the potential risk from a 21-day exposure duration using a 3-week rolling average (sliding by day) across the year, were also all below 100% of the steady state PAD for food (ssPAD_{food}) at the 99.9th percentile of exposure and are not of concern. The population with the highest risk estimate was children (1–2 years old) at 9.7% ssPAD_{food}.

Although EPA’s most recent risk assessment calculated two sets of risk estimates as a result of the dual approach to assess the range of risks that would occur if the Agency determined reliable data existed to support a 1X FQPA safety factor, EPA has determined that it is appropriate to retain the 10X FQPA safety factor, see Unit VI.C.3. Therefore, the risk estimates associated with the 1X FQPA are not relevant to today’s action.

B. Non-Occupational, Non-Dietary (Residential) Risks

Because there are some uses of chlorpyrifos that may result in residential exposures, EPA assessed risk from those uses. All residential post-application risk estimates for the registered uses of chlorpyrifos were

below the Agency's level of concern. (Ref. 9 at 38). The residential post-application LOC for children is 40, and the lowest risk estimate for children (11 to less than 16 years old) was 1,200; the residential post-application LOC for adults is 100, and the MOE is 1,000. Because the calculated MOEs are above the Agency's level of concern, there are no risks of concern from residential exposures.

C. Risks From Drinking Water

As noted above, the Agency aggregated exposures to chlorpyrifos from food and residential exposures and calculated the DWLOC, *i.e.*, the amount of drinking water exposures that would be considered safe. The Agency calculated acute and steady state DWLOCs for infants (less than 1 year old); children (1 to 2 years old); youths (6–12 years old), and adults (females 13–49 years old), which would be protective of other subpopulations. The most sensitive acute DWLOC was 23 ppb chlorpyrifos oxon, and the most sensitive steady state DWLOC was 4 ppb.

As indicated above in Unit VII.B.2., the Agency estimated drinking water contributions from registered uses of chlorpyrifos in its 2016 DWA. That document indicated that EDWCs exceed the DWLOC of 4.0 ppb on a national level and in every region of the United States. (Ref. 28).

While the 2020 DWA produced estimated drinking water concentrations that were below the DWLOC of 4.0 ppb, those EDWCs were contingent upon a limited subset of chlorpyrifos use. 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. When one assesses the potential of all currently registered uses nationwide and in specific geographical areas, as was done in the 2016 DWA, the estimates of drinking water concentrations exceed the DWLOC of 4.0 ppb, in certain vulnerable watersheds across the United States.

D. Aggregate Exposure and Determination Concerning Safety

As noted above, in accordance with FFDCA section 408(b)(2), EPA must, when establishing or leaving in effect tolerances for residues of a pesticide chemical, determine that the tolerances are safe. That is, EPA must determine that “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.” (21 U.S.C. 346a(b)(2)).

As discussed earlier in this Unit, exposures from food and non-occupational exposures individually or together do not exceed EPA's levels of concern. The Agency determined that risks from exposures to chlorpyrifos residues in food comprised 3.2% of the aPAD for females (13–49 years old) and 9.7% of the ssPAD for children (1–2 years old), the highest exposed subpopulations. Combining those exposures with relevant residential exposures, the Agency calculated the allowable levels of drinking water concentrations. Based on the Agency's assessment of drinking water concentrations based on the currently registered uses, however, drinking water exposures significantly add to those risks. When considering the drinking water contribution from currently registered uses, the Agency's levels of concern are exceeded when combined with food and residential exposures.

As indicated above, the Agency calculated acute and steady-state DWLOCs, and the lowest DWLOC is for steady-state exposures to infants at 4.0 ppb; therefore, any EDWCs of chlorpyrifos oxon exceeding 4.0 ppb indicate that aggregate exposures of chlorpyrifos would be unsafe. The Agency's 2016 DWA demonstrates that DWLOC will be exceeded for some people whose drinking water is derived from certain vulnerable watersheds throughout the United States, which means that drinking water contributions will result in aggregate exposures that exceed the Agency's determined safe level of exposure. When taking into consideration aggregate exposures based on current labeled uses, the EDWCs exceed the DWLOC of 4.0 ppb. For example, as noted above in Unit VII.B.2., the 2016 DWA presented EDWCs for uses of chlorpyrifos, including concentrations based on use on golf courses and agricultural crops. For those uses alone, the Agency estimated concentrations exceeding 4.0 ppb in every region in the country; See Table 25 of the 2016 DWA. (Ref. 28 at

73–74.) Comparing the calculated EDWCs from the 2016 DWA with the DWLOC calculated in the 2020 HHRA shows that drinking water concentrations from chlorpyrifos uses will exceed the safe allowable level for contributions from drinking water. This means that aggregate exposure (food, drinking water, and residential exposures) exceeds the Agency's safe level for chlorpyrifos exposure. Because the FFDCA requires EPA to aggregate all dietary and non-occupational exposure, EPA cannot conclude that there is a reasonable certainty that no harm will result from aggregate exposure to chlorpyrifos residues when taking into consideration all labeled uses.

It is worth noting that the Agency's Proposed Interim Registration Review Decision (PID) recognized that there might be limited combinations of uses in certain geographic areas that could be considered safe, if the assessment only includes those specific uses in those areas. The PID noted that “[w]hen considering all currently registered agricultural and non-agricultural uses of chlorpyrifos, aggregate exposures are of concern. If considering only the uses that result in DWLOCs below the EDWCs, aggregate exposures are not of concern.” (Ref. 32 at 19). The PID proposed limiting chlorpyrifos applications to specific crops in certain regions where the EDWCs for those uses were calculated to be lower than the DWLOC. (*Id.* at 40). The Agency's ability to make the safety finding for any remaining uses would be contingent upon significant changes to the existing registrations, including use cancellations, geographical limitations, and other label changes.

Consequently, while the 2020 PID suggested that there may be limited combinations of uses that could be safe, FFDCA section 408(b)(2) requires EPA to aggregate all dietary and non-occupational exposures to chlorpyrifos in making a safety finding. Without effective mitigation upon which to base a reduced aggregate exposure calculation, the products as currently registered present risks above the Agency's levels of concern. Based on the data available at this time and the aggregate exposures expected from currently registered uses, the Agency cannot, at this time, determine that aggregate exposures to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe. Accordingly, as directed by the statute and in compliance with the Court's order, EPA is revoking all chlorpyrifos tolerances.

IX. Procedural Matters

A. When do these actions become effective?

The revocations of the tolerances for all commodities will become effective on February 28, 2022. The Agency has set the expiration date for these tolerances to satisfy its international trade obligations described in Unit X.

Any commodities listed in this rule treated with the pesticide subject to this rule, and in the channels of trade following the tolerance revocations, shall be subject to FFDC section 408(l)(5). Under this section, any residues of these pesticides in or on such food shall not render the food adulterated so long as it is shown to the satisfaction of the Food and Drug Administration that:

1. The residue is present as the result of an application or use of the pesticide at a time and in a manner that was lawful under FIFRA, and

2. The residue does not exceed the level that was authorized at the time of the application or use to be present on the food under a tolerance or exemption from tolerance that was in effect at the time of the application. Evidence to show that food was lawfully treated may include records that verify the dates when the pesticide was applied to such food.

B. Response to Comments

Today's action responds to the Ninth Circuit's order to issue a final rule in response to the 2007 Petition. As such this rule is not finalizing the proposal published in the **Federal Register** issue of November 6, 2015, nor is it implementing or resolving any registration review activity. Thus, this document is not responding to comments received on the 2015 proposal or the most recent registration review documents. Those activities are separate and apart from the procedural posture of this final rule action. Moreover, as the registration review process is ongoing, including a separate review of the comments submitted, the Agency intends to respond to the most recent comments in as part of that process, rather than in this rule.

C. Are the Agency's actions consistent with international obligations?

The tolerance revocations in this final rule are not discriminatory and are designed to ensure that both domestically produced and imported foods meet the food safety standard established by the FFDC. The same food safety standards apply to domestically produced and imported foods.

EPA considers Codex Maximum Residue Limits (MRLs) in setting U.S. tolerances and in reassessing them. Codex MRLs are established by the Codex Committee on Pesticide Residues, a committee within the Codex Alimentarius Commission, an international organization formed to promote the coordination of international food standards. The FFDC requires EPA to take Codex MRLs into consideration when establishing new tolerances, and it is EPA's policy to harmonize U.S. tolerances with Codex MRLs to the extent possible, provided that the MRLs achieve the level of protection required under FFDC. In the current instance, EPA has determined that the current U.S. tolerances for chlorpyrifos are not safe and must be revoked. EPA has developed guidance concerning submissions for import tolerance support (65 FR 35069, June 1, 2000) (FRL-6559-3).

Under the World Trade Organization Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), to which the United States is a party, Members are required to, except in urgent circumstances, "allow a reasonable interval between the publication of a sanitary or phytosanitary regulation and its entry into force in order to allow time for producers in exporting Members, and particularly in developing country Members, to adapt their products and methods of production to the requirements of the importing Member." (Ref. 33). The WTO has interpreted the phrase "reasonable interval" to mean normally a period of not less than six months. (Ref. 34). In accordance with its obligations, EPA intends to notify the WTO of this regulation and is providing a "reasonable interval" by establishing an expiration date for the existing tolerances to allow those tolerances to remain in effect for a period of six months after the effective date of this final rule. After the six-month period expires, the tolerances for residues chlorpyrifos in or on food will no longer be in effect.

X. Statutory and Executive Order Reviews

Additional information about these statutes and Executive Orders can be found at <https://www.epa.gov/laws-regulations-and-executive-orders>.

A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulations and Regulatory Review

The Office of Management and Budget (OMB) has exempted tolerance

regulations from review under Executive Order 12866, entitled Regulatory Planning and Review (58 FR 51735, October 4, 1993). Because this action has been exempted from review under Executive Order 12866, this final rule is not subject to Executive Order 13563 (76 FR 3821, January 21, 2011).

B. Paperwork Reduction Act (PRA)

This final rule does not contain any information collection activities subject to OMB review and approval under the PRA, 44 U.S.C. 3501 *et seq.* An agency may not conduct or sponsor, and a person is not required to respond to a collection of information that requires OMB approval under PRA, unless it has been approved by OMB and displays a currently valid OMB control number. The OMB control numbers for EPA's regulations in title 40 of the CFR, after appearing in the **Federal Register**, are listed in 40 CFR part 9, and included on the related collection instrument or form, if applicable.

C. Regulatory Flexibility Act (RFA)

The RFA, 5 U.S.C. 601 *et seq.*, generally requires an agency to prepare a regulatory flexibility analysis of any rule subject to notice and comment rulemaking requirements under the Administrative Procedures Act or any other statute. Since this rule, which is issued under FFDC section 408(d)(4)(A)(i) (21 U.S.C. 346a(d)(4)(A)(i)) directly in response to a petition under FFDC section 408(d), does not require the issuance of a proposed rule, the RFA requirements do not apply.

D. Unfunded Mandates Reform Act (UMRA)

EPA has determined that this action does not impose any enforceable duty, contain any unfunded mandate, or otherwise have any effect on small governments subject to the requirements of UMRA sections 202, 203, 204, or 205 (2 U.S.C. 1501 *et seq.*).

E. Executive Order 13132: Federalism

This action will not have federalism implications because it is not expected to have a substantial direct effect on States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government, as specified in Executive Order 13132 (64 FR 43255, August 10, 1999). This final rule directly regulates growers, food processors, food handlers and food retailers, not States. This action does not alter the relationships or distribution of power and responsibilities established

by Congress in the preemption provisions of section 408(n)(4) of the FFDCA.

F. Executive Order 13175: Consultation and Coordination With Indian Tribal Governments

For the same reasons, this action will not have Tribal implications because it is not expected to have substantial direct effects on Indian Tribes, significantly or uniquely affect the communities of Indian Tribal governments, and does not involve or impose any requirements that affect Indian Tribes. Accordingly, the requirements of Executive Order 13175 (65 FR 67249, November 9, 2000), do not apply to this action.

G. Executive Order 13045: Protection of Children From Environmental Health and Safety Risks

This action is not subject to Executive Order 13045 (62 FR 19885, April 23, 1997), because this is not an economically significant regulatory action as defined by Executive Order 12866, and this action does not address environmental health or safety risks disproportionately affecting children.

H. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution, or Use

This action is not subject to Executive Order 13211 (66 FR 28355, May 22, 2001), because this action is not a significant regulatory action under Executive Order 12866.

I. National Technology Transfer and Advancement Act (NTTAA)

In addition, since this action does not involve any technical standards, NTTAA section 12(d), 15 U.S.C. 272 note, does not apply to this action.

J. Executive Order 12898: Federal Actions To Address Environmental Justice in Minority Populations and Low-Income Populations

This action does not entail special considerations of environmental justice related issues as delineated by Executive Order 12898 (59 FR 7629, February 16, 1994). Nevertheless, the revocation of the tolerances will reduce exposure to the pesticide and lead to a reduction in chlorpyrifos use on food crops. While EPA has not conducted a formal EJ analysis for this rule, the revocation of tolerances will likely reduce disproportionate impacts on EJ communities that are impacted by chlorpyrifos applications on crops.

K. Congressional Review Act (CRA)

This action is subject to the CRA (5 U.S.C. 801 *et seq.*), and EPA will submit a rule report containing this rule and other required information to each House of the Congress and to the Comptroller General of the United States. This action is not a “major rule” as defined by 5 U.S.C. 804(2).

XI. References

The following is a list of the documents that are specifically referenced in this document. The docket, identified by docket ID number docket number EPA–HQ–OPP–2021–0523, includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. All records in docket are part of the record for this rulemaking. For assistance in locating these other documents, please consult the technical person listed under **FOR FURTHER INFORMATION CONTACT**.

1. The Petition from NRDC and PANNA, EPA’s various responses to it, and the objections submitted on the Petition denial are available in docket number EPA–HQ–OPP–2007–1005 available at <https://www.regulations.gov>.
2. U.S. EPA. Chlorpyrifos Final Work Plan. 2009. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0020>.
3. FIFRA Scientific Advisory Panel (2008). “The Agency’s Evaluation of the Toxicity Profile of Chlorpyrifos.” Report from the FIFRA Scientific Advisory Panel Meeting of September 16–19, 2008. Available at: <https://www.regulations.gov/docket/EPA-HQ-OPP-2008-0274/document>.
4. U.S. EPA (2010). Draft Framework and Case Studies on Atrazine, Human Incidents, and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2009-0851-0004>.
5. U.S. EPA (2016). Office of Pesticide Programs’ Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides. (2016) Available at: <https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf>.
6. FIFRA Scientific Advisory Panel (2012). “Scientific Issues Associated with Chlorpyrifos”. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2012-0040-0029>.
7. U.S. EPA (2014). Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review. Available in docket number EPA–HQ–OPP–2008–0850, <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0195>.
8. U.S. EPA (2016). Scientific Advisory Panel for Chlorpyrifos: Analysis of

Biomonitoring Data. Available at: https://www.epa.gov/sites/default/files/2016-07/documents/chlorpyrifos_sap_april_2016_final_minutes.pdf.

9. U.S. EPA (2020). Chlorpyrifos Human Health Risk Assessment. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0944>.
10. U.S. EPA (2020). Updated Chlorpyrifos Refined Drinking Water Assessment for Registration Review. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0941>.
11. A User’s Guide to Available EPA Information on Assessing Exposure to Pesticides in Food (June 21, 2000). Available at: https://www.doh.wa.gov/Portals/1/Documents/4000/PASW_exposurerefod.pdf.
12. U.S. EPA (2000). Chlorpyrifos Human Health Risk Assessment. Available at: https://archive.epa.gov/scipoly/sap/meetings/web/pdf/hed_ra.pdf.
13. U.S. EPA (2011). Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review. Available in docket number EPA–HQ–OPP–2008–0850, <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0025>.
14. U.S. EPA (2016). Summary Reviews for Additional Epidemiological Literature Studies from Prospective Birth Cohort Studies. Available in docket number EPA–HQ–OPP–2015–0653 at <https://www.regulations.gov/document/EPA-HQ-OPP-2015-0653-0438>.
15. U.S. EPA (2020). The Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment. Available in docket number EPA–HQ–OPP–2020–0263 at <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0033>.
16. U.S. EPA (2020). Transmittal of Meeting Minutes and Final Report of the Federal Insecticide, Fungicide, and Rodenticide Act, Scientific Advisory Panel (FIFRA SAP) Virtual Meeting held on September 15–18, 2020. Available in docket number EPA–HQ–2020–0263 at <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0263-0054>.
17. U.S. EPA (2006). Revised Organophosphorous Pesticide Cumulative Risk Assessment. Available at <http://www.epa.gov/pesticides/cumulative/2006-op/index.htm>.
18. U.S. EPA (2012). Standard Operating Procedures for Residential Pesticide Exposure Assessment https://www.epa.gov/sites/default/files/2015-08/documents/usepa-opp-hed_residential_sops_oct2012.pdf.
19. FIFRA Scientific Advisory Panel (2002). “Organophosphate Pesticides: Preliminary OP Cumulative Risk Assessment.” Information on how to obtain the meeting report is available at <http://www2.epa.gov/sap/fifra-scientific-advisory-panel-meetings>.
20. U.S. EPA (2000). Choosing a Percentile of Acute Dietary Exposure as a Threshold of Regulatory Concern. Available at:

- https://www.epa.gov/sites/production/files/2015-07/documents/trac2b054_0.pdf.
21. EPA's Exposure Factors Handbook. Available at: <https://www.epa.gov/expobox/about-exposure-factors-handbook>.
 22. U.S. EPA (2014). Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. Available at: <https://www.epa.gov/sites/default/files/2015-01/documents/ddef-final.pdf>.
 23. U.S. EPA (2014). Chlorpyrifos Acute and Steady Dietary (Food Only) Exposure Analysis to Support Registration Review. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0197>.
 24. U.S. EPA (2020). Framework for Conducting Pesticide Drinking Water Assessments for Surface Water. Environmental Fate and Effects Division. Office of Pesticide Programs. Office of Chemical Safety and Pollution Prevention. U.S. Environmental Protection Agency. Available at: <https://www.epa.gov/sites/default/files/2020-09/documents/framework-conducting-pesticide-dw-sw.pdf>.
 25. FIFRA Scientific Advisory Panel (2019) "Approaches for Quantitative Use of Surface Water Monitoring Data in Pesticide Drinking Water Assessments." Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2019-0417-0019>.
 26. U.S. EPA (2001). General Principles for Performing Aggregate Exposure and Risk Assessments. Available at: <https://www.epa.gov/sites/default/files/2015-07/documents/aggregate.pdf>.
 27. U.S. EPA (2020). Appendix B. Case Study for Integrating a Distributional Approach to Using Percent Crop Area (PCA) and Percent Crop Treated (PCT) into Drinking Water Assessment. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2020-0279-0002>.
 28. U.S. EPA (2016). Chlorpyrifos Refined Drinking Water Assessment for Registration Review. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2015-0653-0437>.
 29. U.S. EPA (2014). Chlorpyrifos Updated Drinking Water Assessment for Registration Review. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0198>.
 30. U.S. EPA (2015). Proposed Rule: Tolerance Revocations: Chlorpyrifos. Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2015-0653-0001>.
 31. U.S. EPA (2011). Finalization of Guidance on Incorporation of Water Treatment Effects on Pesticide Removal and Transformations in Drinking Water Exposure Assessments. Available at: <https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/finalization-guidance-incorporation-water-treatment>.
 32. U.S. EPA (2020). Chlorpyrifos Proposed Interim Registration Review Decision.

Available at: <https://www.regulations.gov/document/EPA-HQ-OPP-2008-0850-0971>.

33. For more information on World Trade Organization's Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement), please see: https://www.wto.org/english/tratop_e/sps_e/spsagr_e.htm.
34. For more information on World Trade Organization (2001) Implementation-Related Issues and Concerns, please see: <https://docs.wto.org/dol2fe/Pages/SS/directdoc.aspx?filename=Q:/WT/Min01/17.pdf&Open=True>.

List of Subjects in 40 CFR Part 180

Environmental protection, Administrative practice and procedure, Agricultural commodities, Pesticides and pests, Reporting and recordkeeping requirements.

Dated: August 18, 2021.

Edward Messina,
Director, Office of Pesticide Programs.

Therefore, for the reasons set forth in the preamble, 40 CFR part 180 is amended as follows:

PART 180—[AMENDED]

■ 1. The authority citation for part 180 continues to read as follows:

Authority: 21 U.S.C. 321(q), 346a and 371.

■ 2. In § 180.342, add introductory text to read as follows:

§ 180.342 Chlorpyrifos; tolerances for residues.

This section and all tolerances contained herein expire and are revoked on February 28, 2022.

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[FR Doc. 2021-18091 Filed 8-27-21; 8:45 am]

BILLING CODE 6560-50-P

DEPARTMENT OF DEFENSE

Defense Acquisition Regulations System

48 CFR Parts 212, 225 and 252

[Docket DARS-2020-0039]

RIN 0750-AL15

Defense Federal Acquisition Regulation Supplement: Improved Energy Security for Main Operating Bases in Europe (DFARS Case 2020-D030)

AGENCY: Defense Acquisition Regulations System, Department of Defense (DoD).

ACTION: Final rule.

SUMMARY: DoD is issuing a final rule amending the Defense Federal

Acquisition Regulation Supplement (DFARS) to implement a section of the National Defense Authorization Act for Fiscal Year 2020. This section prohibits contracts for the acquisition of furnished energy for a covered military installation in Europe that is sourced from inside the Russian Federation.

DATES: Effective August 30, 2021.

FOR FURTHER INFORMATION CONTACT: Ms. Kimberly Bass, telephone 571-372-6174.

SUPPLEMENTARY INFORMATION:

I. Background

DoD published a proposed rule in the **Federal Register** at 86 FR 3935 on January 15, 2021, to amend the DFARS to implement section 2821 of the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2020 (Pub. L. 116-92). Section 2821 prohibits use of energy sourced from inside the Russian Federation in an effort to promote energy security in Europe. The prohibition applies to all forms of energy "furnished to a covered military installation" as that term is defined in the statute. No public comments were received in response to the proposed rule.

II. Discussion and Analysis

A. Summary of Significant Changes

No changes are made to the final rule as a result of public comments.

B. Other Changes

One change is made to the rule as proposed to clarify the same language that appears in section 225.7019-2, paragraph (b); the provision 252.225-7053, paragraph (b)(2); and clause 252.225-7054, paragraph (b)(2). In all three locations, the statement "Does not apply to a third party that uses it to create some other form of energy (e.g., heating, cooling, or electricity)" is changed to read "Does not apply to energy converted by a third party into another form of energy and not directly delivered to a covered military installation." No other changes are made to the rule.

III. Applicability to Contracts At or Below the Simplified Acquisition Threshold and for Commercial Items, Including Commercially Available Off-the-Shelf Items

This DFARS rule implements section 2821 of the NDAA for FY 2020 (Pub. L. 116-92). Section 2821 prohibits use of energy sourced from inside the Russian Federation unless a waiver is approved by the head of the contracting activity. To implement section 2821, this rule creates a new solicitation provision and