FOR PUBLICATION

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

LEAGUE OF UNITED LATIN AMERICAN CITIZENS; PESTICIDE ACTION NETWORK NORTH AMERICA; NATURAL RESOURCES DEFENSE COUNCIL; CALIFORNIA RURAL LEGAL ASSISTANCE FOUNDATION; FARMWORKERS ASSOCIATION OF FLORIDA; FARMWORKER JUSTICE; LABOR COUNCIL FOR LATIN AMERICAN ADVANCEMENT; LEARNING DISABILITIES ASSOCIATION OF AMERICA; NATIONAL HISPANIC MEDICAL ASSOCIATION; PINEROS Y CAMPESINOS UNIDOS DEL NOROESTE; UNITED FARM WORKERS; GREENLATINOS, *Petitioners*, v. MICHAEL S. REGAN, Administrator, United States Environmental Protection Agency; U.S. ENVIRONMENTAL PROTECTION AGENCY, *Respondents.*	No. 19-71979 EPA No. EPA-HQ-OPP-2007-1005

STATE OF NEW YORK; STATE OF CALIFORNIA; STATE OF WASHINGTON; STATE OF MARYLAND; STATE OF VERMONT; COMMONWEALTH OF MASSACHUSETTS,
Petitioners,

DISTRICT OF COLUMBIA; STATE OF HAWAII; STATE OF OREGON,
Intervenors,

v.

MICHAEL S. REGAN, Administrator, United States Environmental Protection Agency; U.S. ENVIRONMENTAL PROTECTION AGENCY,
Respondents.

No. 19-71982

EPA No. EPA-HQ-OPP-2007-1005

OPINION

On Petition for Review of an Order of the Environmental Protection Agency

Argued and Submitted July 28, 2020
San Francisco, California

Filed April 29, 2021

Before: Jay S. Bybee and Jacqueline H. Nguyen, Circuit Judges, and Jed S. Rakoff,* District Judge.

Opinion by Judge Rakoff;
Dissent by Judge Bybee

SUMMARY**

Environmental Protection Agency

The panel granted petitions for review, vacated the Environmental Protection Agency ("EPA")'s 2017 Order and 2019 Order, and remanded with instructions to the EPA in cases challenging the EPA's regulation of the pesticide chlorpyrifos.

The EPA has recognized that when pregnant mothers are exposed to chlorpyrifos residue, this likely harms infants *in utero*. This proceeding began in 2007, when two environmental non-profit organizations filed a petition asking the EPA to prohibit foods that contain residue of the insecticide chlorpyrifos. The EPA declined to take final action on the 2007 Petition for more than a decade. This Court issued multiple writs of mandamus requiring the EPA to move forward. In 2017, the EPA denied the 2007 Petition, and in 2019 denied all objections to that decision.

* The Honorable Jed S. Rakoff, United States District Judge for the Southern District of New York, sitting by designation.

** This summary constitutes no part of the opinion of the court. It has been prepared by court staff for the convenience of the reader.

The panel held that the EPA had abdicated its statutory duty under the Federal Food, Drug and Cosmetic Act ("FFDCA"). The panel held that the EPA spent more than a decade assembling a record of chlorpyrifos's ill effects and repeatedly determined, based on that record, that it could not conclude, to the statutorily required standard of reasonable certainty, that the present tolerances caused no harm. Rather than ban the pesticide or reduce the tolerances to levels that the EPA could find were reasonably certain to cause no harm, the EPA sought to evade through delay tactics its plain statutory duty. Because the FFDCA permitted no further delays, the panel ordered the EPA within 60 days after issuance of the mandate either to modify chlorpyrifos's tolerances and concomitantly publish a finding that the modified tolerances are safe, including for infants and children – or to revoke all chlorpyrifos tolerances. The panel also ordered the EPA to correspondingly modify or cancel related Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA") regulations for food use in a timely fashion consistent with the requirements of 21 U.S.C. § 346a(a)(1).

Specifically, the panel first considered whether the EPA lawfully denied the 2007 Petition. The panel rejected the EPA's argument that it could leave in effect tolerances, without a new safety finding, when the EPA concluded the petition contained insufficient evidence for the EPA to undertake proceedings to revoke or modify tolerances. The panel held, first, once the EPA became aware, through a petition or otherwise, of genuine questions about the safety of an existing tolerance, the EPA had its own continuing duty under the FFDCA to determine whether a tolerance that was once thought to be safe still is. Here, the EPA's own studies and pronouncements still in effect showed that it regarded chlorpyrifos as harmful at levels below the existing tolerances. Second, the 2007 Petition, under the EPA's own

regulations, contained more than sufficient evidence to undertake a safety review, and the EPA recognized as much. The panel held that when the EPA publishes a petition seeking revocation of a tolerance and later takes final action denying that petition, the EPA leaves that tolerance in effect. The EPA can only do so if it finds the tolerance to be safe for the general population and for infants and children. The EPA failed to make such findings, directly contrary to the FFDCA.

The panel held that even if the FFDCA did not require a safety finding here, the EPA's denial of the 2007 Petition was arbitrary and capricious. The panel rejected the EPA's four objections to the data.

The panel held that its remand with specific instructions did not raise due process concerns. On this record, immediate issuance of a final regulation was the only reasonable action, and the panel ordered the EPA to do so. The panel clarified that this was not an open-ended remand, or a remand for further factfinding.

Dissenting, Judge Bybee wrote that the majority opinion erred by misreading the FFDCA, and misallocating the risk of nonpersuasion; overruling the EPA's judgment on the validity and weight to be given technical evidence within the EPA's expertise; and, by its decision to give the EPA 60 days to issue a final decision, likely predetermining EPA's option.

COUNSEL

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OPINION

RAKOFF, District Judge:

This dispute concerning the documented health risks posed by a widely used pesticide, chlorpyrifos, has been before this Court more than a half-dozen times. The Environmental Protection Agency ("EPA" or the "Agency") has recognized that when pregnant mothers are exposed to chlorpyrifos residue, this likely harms infants *in utero*. Nevertheless, in derogation of the statutory mandate to ban pesticides that have not been proven safe, the EPA has failed to act, requesting extension after extension. The Agency's present position is effectively more of the same.

The proceeding began in 2007, when two environmental non-profit organizations – Pesticide Action Network North America ("PANNA") and the Natural Resources Defense Council, Inc. ("NRDC") – filed a petition (the "2007 Petition") asking the EPA to prohibit foods that contain any residue of the insecticide chlorpyrifos. Then, and now, the EPA has permitted distribution of food containing chlorpyrifos residue as long as the residue is less than a limit known as a "tolerance," which varies depending on the food. The 2007 Petition argued that, even at levels beneath these tolerances, chlorpyrifos poses neurodevelopmental risks, especially to infants and children.

The Federal Food, Drug and Cosmetic Act ("FFDCA") provides that the EPA's "Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke

a tolerance if the Administrator determines it is not safe."[1] The statute also requires that the EPA "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue" and "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children."[2]

Since 2007, the evidence of harm has continued to build, primarily through two kinds of studies: experimental studies on live mice and rats and epidemiological studies tracking humans who were exposed to chlorpyrifos *in utero*. Between 2007 and 2016, the EPA published several Human Health Risk Assessments regarding chlorpyrifos and convened its Scientific Advisory Panel ("SAP") several times. Those assessments and SAP reviews increasingly recognized the persuasiveness of the studies showing chlorpyrifos's risks. Nevertheless, the EPA declined to take final action on the 2007 Petition for more than a decade. Eventually, PANNA, NRDC, and others sought judicial relief, and this Court issued multiple writs of mandamus requiring the EPA to move forward. But, *festina lente*, the EPA continued to delay ruling on the 2007 Petition. This, moreover, was despite the fact that in November 2015, the EPA published a Notice of Proposed Rulemaking that proposed to revoke all chlorpyrifos tolerances because the EPA could not find them to be safe. Similarly, in 2016, the EPA issued a Revised Human Health Risk Assessment

[1] 21 U.S.C. § 346a(b)(2)(A)(i).

[2] *Id.* § 346a(b)(2)(C)(i)–(ii).

finding that the present tolerances are "not sufficiently health protective."[3]

In 2017, the EPA, pursuant to a court-set deadline, finally ruled on the 2007 Petition. But in the very face of its own prior acknowledgements of the health risks posed by chlorpyrifos, the EPA denied the 2007 Petition, and in 2019 denied all objections to that decision. In reality, however, this was just one more attempt at delay, because the EPA did not conclude that the tolerances were safe, but simply denied the Petition on the ground that the EPA would forgo further consideration of the question of safety until chlorpyrifos underwent a registration re-review under a separate statute, which could be as late as 2022. As explained below, this delay tactic was a total abdication of the EPA's statutory duty under the FFDCA.

In short, the EPA has spent more than a decade assembling a record of chlorpyrifos's ill effects and has repeatedly determined, based on that record, that it cannot conclude, to the statutorily required standard of reasonable certainty, that the present tolerances are causing no harm. Yet, rather than ban the pesticide or reduce the tolerances to levels that the EPA *can* find are reasonably certain to cause no harm, the EPA has sought to evade, through one delaying tactic after another, its plain statutory duties. The FFDCA permits no further delay. Accordingly, for the reasons that follow, the Court grants the petitions for review and orders the EPA within 60 days after the issuance of the mandate either to modify chlorpyrifos tolerances *and* concomitantly publish a finding that the modified tolerances are safe,

[3] Chlorpyrifos; Tolerance Revocations; Notice of Data Availability and Request for Comment, 81 Fed. Reg. 81,049, 81,050 (Nov. 17, 2016) (hereinafter "2016 Notice of Data Availability").

including for infants and children – or to revoke all chlorpyrifos tolerances. The Court also orders the EPA to correspondingly modify or cancel related FIFRA registrations for food use in a timely fashion consistent with the requirements of 21 U.S.C. § 346a(a)(1).

BACKGROUND

I. The EPA's Duty to Regulate Pesticides

Congress requires the EPA to regulate the use of pesticides on food pursuant to the FFDCA. Congress also requires the EPA to regulate the use of pesticides more generally under the Federal Insecticide, Fungicide and Rodenticide Act ("FIFRA"). This case principally concerns the FFDCA.

The FFDCA begins with a general rule that food containing pesticide residue is unsafe and prohibited.[4] Congress empowered the EPA to make exceptions to that rule by promulgating "tolerances" for a pesticide – *i.e.*, threshold levels of pesticide residue that the EPA is reasonably certain will cause no harm.[5] If the EPA promulgates a tolerance for a pesticide, then food may contain residue of that pesticide in an amount not exceeding the applicable tolerance.[6]

The EPA's discretion to set such tolerances is circumscribed, however, by an uncompromisable limitation:

[4] *Id.* §§ 331, 342(a)(2)(B), 346a(a)(1). The FFDCA applies only to food and other products in interstate commerce. *See* 21 U.S.C. § 331.

[5] *Id.* § 346a(b)(1), (b)(2)(A).

[6] *Id.* § 346a(a)(4).

the pesticide must be determined to be safe for human beings. The EPA "may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food *only* if the Administrator determines that the tolerance is safe."[7] Furthermore, following enactment of the Food Quality Protection Act of 1996 ("FQPA"), it is now clear that the EPA must look beyond food to consider all of the ways someone might be exposed to a pesticide, "including all anticipated dietary exposures and all other exposures for which there is reliable information."[8] The EPA can determine that a tolerance is safe only if "there is a *reasonable certainty* that no harm will result from *aggregate* exposure to the pesticide chemical residue."[9]

In addition to requiring this general safety finding, the FFDCA also conditions the EPA's authority to set or leave in effect a tolerance on its determination that the tolerance is safe for infants and children. "In establishing, modifying, leaving in effect, or revoking a tolerance . . . , the Administrator . . . shall . . . ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue," and shall "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children."[10] If a tolerance is not safe – in other words, if the EPA cannot determine that there is a reasonable certainty of no harm across all sources of exposure for infants, children, and adults – then the EPA no longer has discretion. Rather, the

[7] *Id.* § 346a(b)(2)(A)(i) (emphasis added).

[8] *Id.* § 346a(b)(2)(A)(ii).

[9] *Id.* (emphases added).

[10] *Id.* § 346a(b)(2)(C)(ii).

law commands that the EPA "shall modify or revoke [the] tolerance."[11]

The FFDCA authorizes "[a]ny person [to] file . . . a petition proposing the issuance of a regulation establishing, modifying, or revoking a tolerance."[12] The EPA, by regulation, may dictate what a petition seeking revocation of a tolerance must contain.[13] Pursuant to that authority, the EPA requires that a petition state "reasonable grounds for the action sought," including "an assertion of facts."[14] If the EPA determines that a petition has met the threshold requirements, then it must publish the petition within 30 days.[15] "[A]fter giving due consideration to a petition . . . and any other information available to the Administrator," the EPA "shall" do one of three things: "issue a final regulation (which may vary from that sought by the petition) establishing, modifying, or revoking a tolerance . . . (which final regulation shall be issued without further notice and without further period for public comment)," "issue a proposed regulation . . . and thereafter issue a final regulation," or "issue an order denying the petition."[16] If the EPA denies a petition, "any person may file objections

[11] *Id.* § 346a(b)(2)(A)(i).

[12] *Id.* § 346a(d)(1).

[13] *Id.* § 346a(d)(2)(B).

[14] 40 C.F.R. § 180.32(b).

[15] 21 U.S.C. § 346a(d)(3).

[16] *Id.* § 346a(d)(4)(A).

thereto with the Administrator."[17] The Administrator "shall issue an order stating the action taken upon each . . . objection" "[a]s soon as practicable."[18] Those affected may seek "judicial review . . . in the United States Court of Appeals."[19]

Separately, the EPA also regulates pesticides pursuant to FIFRA. Under FIFRA, pesticides must be registered by the EPA before they can be distributed or sold.[20] To register a pesticide, the EPA must determine, among other things, that it does not have "unreasonable adverse effects on the environment."[21] FIFRA defines "unreasonable adverse effects" to include "a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with" the standards of the FFDCA.[22] In other words, FIFRA incorporates the FFDCA safety standard for food uses, among other considerations. FIFRA requires the EPA to reevaluate pesticides as part of a registration review every fifteen years.[23]

[17] *Id.* § 346a(g)(2)(A).

[18] *Id.* § 346a(g)(2)(C).

[19] *Id.* § 346a(h)(1).

[20] *See* 7 U.S.C. § 136a(a).

[21] *Id.* § 136a(c)(5)(C)–(D).

[22] *Id.* § 136(bb).

[23] *See id.* §§ 136a(c)(1)(F)(iii), (g)(1)(A), 136a-1(a).

II. This Administrative Proceeding and Related Litigation

This administrative proceeding began with the filing of the 2007 Petition, which sought revocation of all tolerances and registrations for chlorpyrifos. Chlorpyrifos is an organophosphate pesticide. Organophosphates were first developed as toxic nerve agents for potential use in chemical warfare during World War II, and chlorpyrifos was initially registered as a pesticide in the United States in 1965. Since then, farmers have used chlorpyrifos to protect dozens of types of crops. As of 2017, "[b]y pounds of active ingredient, it [was] the most widely used conventional insecticide in the country."[24] Nevertheless, in 2019, California (and the European Union) announced they would ban the sale of chlorpyrifos.[25]

Chlorpyrifos disrupts the functioning of acetylcholinesterase ("AChE"), a crucial enzyme that breaks down the neurotransmitter acetylcholine.[26] In setting

[24] Chlorpyrifos; Order Denying PANNA and NRDC's Petition to Revoke Tolerances, 82 Fed. Reg. 16,581, 16,584 (Apr. 5, 2017) (hereinafter "2017 Order").

[25] Press Release, Cal. Env't Prot. Agency & Cal. Dep't of Pesticide Regul., *Agreement Reached to End Sale of Chlorpyrifos in California by February 2020* (Oct. 9, 2019), https://www.cdpr.ca.gov/docs/pressrls/2019/100919.htm; Stephen Gardner, *EU to Ban Chlorpyrifos Pesticide Starting in February*, Bloomberg L. News (Dec. 6, 2019, 6:43 AM), https://news.bloomberglaw.com/environment-and-energy/eu-to-ban-chlorpyrifos-pesticide-starting-in-february.

[26] *See* EPA, Office of Prevention, Pesticides, and Toxic Substances, EPA 738-R-01-007, Interim Reregistration Eligibility Determination for Chlorpyrifos 2 (Feb. 2002) ("Chlorpyrifos can cause [AChE] inhibition in humans; that is, it can overstimulate the nervous system causing

chlorpyrifos tolerances, the EPA must determine the greatest exposure amount that poses no risk of harm, which is known as a "point of departure." Since enactment of the FQPA, the EPA has tied the chlorpyrifos point of departure directly to acute AChE inhibition, finding that exposure to chlorpyrifos residue on food would be unsafe if aggregate exposure across all sources caused more than 10% acute AChE inhibition.

However, for decades, the EPA has itself expressed concerns that chlorpyrifos might also be causing harm through a different mechanism: neurotoxic effects that are especially harmful to infants and children.[27] The 2007 Petition was partly based on these concerns. Yet, despite the EPA's expressed concerns, the EPA repeatedly failed to act on the 2007 Petition until this Court compelled it to do so. The following is a chronological summary both of the EPA's assessment of chlorpyrifos's safety and of this dispute.

A. 2000–2006: The EPA Finds Certain Chlorpyrifos Tolerances Safe, Despite Concerns

Between 2000 and 2006, even before the Petition was filed, the EPA began taking steps to reduce exposure to chlorpyrifos as part of its reevaluation of chlorpyrifos's safety, as required by the FQPA. The FQPA imposed the requirements, still included in the FFDCA today, that the

nausea, dizziness, confusion, and at very high exposures (e.g., accidents or major spills), respiratory paralysis and death.").

[27] This different mechanism of harm might still relate to AChE inhibition; the EPA has considered the possibility that *chronic* AChE inhibition at levels of less than 10% might cause permanent damage. Herein, unless stated otherwise, AChE inhibition means *acute* AChE inhibition of 10% or more.

EPA (1) consider proof of safety as an absolute prerequisite to establishing or leaving in effect a tolerance, without balancing it against other factors; (2) assess a pesticide's cumulative exposure from multiple sources (*e.g.*, drinking water as well as food); and (3) specifically assess the pesticide's potential risks to children. The FQPA also required the EPA to reassess the safety of all then-authorized pesticides using this new standard.

During this period, the EPA began to express concerns that chlorpyrifos might be causing harms through a mechanism other than AChE inhibition. For example, in a 2000 Human Health Risk Assessment, the EPA recognized that studies had preliminarily shown that AChE inhibition might not be the only mechanism of harm.[28]

The EPA also began acting on its concerns about chlorpyrifos safety, in collaboration with the pesticide industry. In 2000, the EPA and the chlorpyrifos technical registrants entered into an agreement regarding chlorpyrifos that eliminated or phased out its use for virtually all residential and termiticide purposes, and on tomatoes and, during the growing season, grapes and apples.[29] In 2002, the

[28] EPA, Office of Pesticide Programs, Human Health Risk Assessment-Chlorpyrifos 4 (June 8, 2000), https://archive.epa.gov/scipoly/sap/meetings/web/pdf/hed_ra.pdf (discussing live animal studies and explaining that "new data in the literature also gave rise to uncertainties such as the suggestion that the inhibition of [AChE] may not be essential for adverse effects on brain development").

[29] Letter to Aaron Colangelo, NRDC, & Margaret Reeves, PANNA, from Steven Bradbury, EPA, re: Chlorpyrifos Petition Dated September 12, 2007 (hereinafter "2007 Petition"), at 6 (July 16, 2012).

EPA announced certain risk mitigation measures, especially for people exposed to chlorpyrifos through their work.[30]

Subject to these changes, however, the EPA determined in February 2002, based upon the evidence then available, that "[d]ietary exposures from eating food crops treated with chlorpyrifos are below the level of concern for the entire U.S. population, including infants and children," and that "[d]rinking water risk estimates . . . are generally not of concern."[31] The EPA reiterated its safety finding in July 2006, stating that chlorpyrifos tolerances "meet the safety standard under Section 408(b)(2) of the FFDCA."[32]

B. 2007: PANNA and NRDC File a Petition to Revoke Tolerances, Citing Mounting Evidence of Harm

In September 2007, PANNA and NRDC filed an administrative petition with the EPA seeking revocation of all chlorpyrifos tolerances under the FFDCA and the cancellation of all of chlorpyrifos's FIFRA registrations. The 2007 Petition asserted that scientific evidence now available showed that the current chlorpyrifos tolerances were not safe, especially for infants and children; indeed, they argued, "no safe level of early-life exposure to

[30] Interim Reregistration Eligibility Decision for Chlorpyrifos, *supra* note 26.

[31] *Id.* at 2.

[32] EPA, Office of Prevention, Pesticides and Toxic Substances, Memo to Jim Jones from Debra Edwards, Finalization of Interim Reregistration Eligibility Decisions and Interim Tolerance Reassessment and Risk Management Decisions for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides 2 (July 31, 2006).

chlorpyrifos can be supported."[33] They cited "[m]any studies published since 2001 [that] report that fetal exposure to chlorpyrifos is more damaging than adult exposure."[34]

The 2007 Petition relied in part upon certain experiments performed on live mice and rats. They were exposed *in utero* to levels of chlorpyrifos below those previously known to cause AChE inhibition. The scientists found marked declines in thinking and movement, indicative of neurological effects. The declines were sex-linked, harming males more than females.

The 2007 Petition also relied upon an epidemiological study, known as the "Columbia Study." Researchers worked with a cohort of pregnant women and their children, collecting data on the mothers' organophosphate exposure (including chlorpyrifos) during pregnancy, and then following the development of the children for many years. Some of the participating children were born before the EPA and the registrants agreed to end residential use of chlorpyrifos, and others were born after. Over time, the researchers found a correlation between prenatal chlorpyrifos exposure and several negative outcomes:

- at age three, lower performance in motor and mental development tests and higher incidences of attention-deficit hyperactivity disorder and autism spectrum disorder;

[33] Marc S. Wu et al., NRDC, & Susan E. Kegley, PANNA, Petition to Revoke All Tolerances and Registrations for the Pesticide Chlorpyrifos 5 (Sept. 12, 2007).

[34] *Id.* at 6.

- at age seven, changes in brain morphology and lower IQ scores; and

- at age eleven, a greater likelihood of mild or moderate tremors.

Like the live animal experiments, the Columbia Study found that *in utero* exposures were harmful even beneath the levels thought to cause notable AChE inhibition and that harms were sex-linked, disproportionately affecting boys.

Two other groups of researchers also conducted epidemiological studies similar to the Columbia Study (the "Mount Sinai Study" and the "CHAMACOS Study"; collectively with the Columbia Study, the "Human Cohort Studies"). The Mount Sinai and CHAMACOS Studies looked at exposure to organophosphate pesticides and, like the Columbia Study, found a correlation between prenatal organophosphate exposure and cognitive impairments in early childhood.[35]

C. 2008–2011: The EPA Preliminarily Links Chlorpyrifos to Neurotoxic Harms in Infants and Children

Within a year of the 2007 Petition, the EPA, in August 2008, published a Science Issue Paper, which reviewed existing scientific studies and "preliminarily concluded that chlorpyrifos likely played a role" in the low birth rate and delays in infant mental development observed in the Human

[35] Although the Mount Sinai Study and the CHAMACOS Study were not cited in the 2007 Petition, they later became part of the administrative record.

Cohort Studies.[36] The EPA recognized that some of these studies found these effects despite lesser AChE inhibition, suggesting there was a different mechanism of harm.[37] However, the paper also noted that it was "not a full and complete risk assessment/characterization," and that the EPA "ha[d] not developed any final conclusions regarding updates to the chlorpyrifos hazard assessment."[38]

In September 2008, the EPA convened a committee of experts known as a Scientific Advisory Panel ("SAP") to peer-review its findings. The 2008 SAP considered "the results of the three [Human Cohort Studies] (with an emphasis on the Columbia [S]tudy) . . . along with the findings from experimental studies in animals," and concluded that "maternal chlorpyrifos exposure would likely be associated with adverse neurodevelopmental outcomes in humans."[39] The SAP "agreed with [the EPA's] conclusion that chlorpyrifos likely played a role in the birth and neurodevelopmental outcomes noted in the three [Human Cohort Studies]."[40]

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[36] Health Effects Division, Office of Pesticide Programs, EPA, Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization 52 (Aug. 21, 2008).

[37] *Id*. at 40–41 & fig.5.

[38] *Id*. at 7.

[39] SAP Minutes No. 2008-04, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos 13 (Sept. 16–18, 2008) (hereinafter "2008 SAP Minutes").

[40] *Id*. at 37.

However, the SAP also posited that the effects might not be entirely attributable to chlorpyrifos; rather, they might also reflect exposure to other AChE-inhibiting insecticides. A majority of SAP members agreed that the adverse outcomes of the Columbia Study were concerning, especially "in light of evidence demonstrating that low levels of exposure to toxicants once thought to have adverse neurodevelopmental effects only at high levels (i.e. lead, mercury, and PCBs) are now known to produce significant effects at lower levels."[41] Nevertheless, the 2008 SAP found that the Human Cohort Studies had "utility for risk characterization, but not as the principal basis for establishing the point of departure."[42]

About three years later, in 2011, the EPA published a Preliminary Human Health Risk Assessment. The EPA discussed the three Human Cohort Studies and noted the 2008 SAP's conclusion that those studies, "in concert with the animal studies[,] indicate that 'maternal chlorpyrifos exposure would likely be associated with adverse

[41] *Id.* at 43–44.

[42] 2007 Petition, *supra* note 29, at 6–7. The Dissent notes that the 2008 SAP expressed "concerns that the Columbia Study—the most robust of the three—did not provide sufficient data to be the sole factor for risk assessment or modifying tolerances and produced uncertainty through its measurement method." Dissent, *infra*, at 91. In fact, although the 2008 SAP recognized that "there were limitations . . . that precluded [the Human Cohort Studies] from being used to directly derive the [point of departure] or the uncertainty factor," it also concluded that the Columbia Study "could be used to determine bounding values for the levels of chlorpyrifos that might cause a measurable effect." 2008 SAP Minutes, *supra* note 39, at 46. Thus, even as early as 2008, the SAP recognized the utility of the Columbia Study for risk assessment.

neurodevelopmental outcomes in humans.'"[43] While the Preliminary Human Health Risk Assessment asserted that the EPA could not yet identify the mechanism of action for neurotoxic harm, nevertheless, it viewed the Human Cohort Studies favorably, describing the Columbia Study as a "natural experiment" since some participants were pregnant before the EPA banned residential use of chlorpyrifos and some were pregnant after the ban.[44] The EPA "intend[ed] to carefully consider the strengths and limitations of the epidemiology studies along with the available empirical data in a full weight of evidence analysis in the final [Human Health Risk Assessment]."[45] Thus, while the EPA continued to use 10% AChE inhibition to set a point of departure, it explained that "ongoing analyses will ensure that [the points of departure] in [its] preliminary assessment are [also] human health protective for neurodevelopmental toxicity that may arise from pre- or postnatal exposure."[46]

[43] Memo from Danette Drew et al. to Tom Myers re: Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review, EPA, at 28 (June 30, 2011).

[44] *Id.* at 31.

[45] *Id.* at 34.

[46] *Id.* at 42.

D. 2012–2015: The EPA Expresses Increasing Certainty That Chlorpyrifos Causes Neurotoxic Effects in Infants and Children

In April 2012, having received no response from the EPA on the pertinent arguments raised in the 2007 Petition,[47] PANNA and NRDC petitioned this Court for a writ of mandamus.

Meanwhile, also in April 2012, the EPA convened another SAP. The 2012 SAP opined with more certainty than the 2008 SAP that multiple "lines of evidence suggest that chlorpyrifos can affect neurodevelopment at levels lower than those associated with AChE inhibition, and that the use of AChE inhibition data may not be the most appropriate for . . . [assessing] the neurodevelopmental risks of chlorpyrifos."[48] The 2012 SAP paid particular attention to the Human Cohort Studies and identified "nine strengths" of them, including, among others, the longitudinal design, the use of biomarkers of exposure (rather than only self-reported exposure), and "the relative consistency of findings in different populations while using similar standardized exposure and outcome measures."[49] The 2012 SAP also identified some shortcomings of the Human Cohort Studies, such as a relatively small sample size and uncertainty

[47] The 2007 Petition raised several other claims, some of which the EPA addressed at earlier points in time, but here petitioners only press the claims related to neurotoxic effects.

[48] SAP Minutes No. 2012-04, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Chlorpyrifos Health Effects 53 (Apr. 10–12, 2012) (hereinafter "2012 SAP Minutes").

[49] *Id.* at 18.

regarding whether harms could be attributed to chlorpyrifos alone. Overall, though, it found that "[t]he strengths of the three studies support the Panel's conclusion."[50]

Specifically, the 2012 SAP, based on its review of all the evidence available at the time, "concur[red] with the 2008 SAP and the Agency in concluding that chlorpyrifos likely plays a role in impacting the neurodevelopmental outcomes examined in the three cohort studies."[51] It noted that the Human Cohort Studies showed potentially serious harms to infants and children, including "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."[52]

Despite all this, the EPA, following issuance of the 2012 SAP report, still did not take final action on the 2007 Petition; but it represented in the mandamus proceedings that it had "a concrete timeline for final agency action that would resolve the 2007 Petition by February 2014."[53] In light of that representation, this Court, in July 2013, denied PANNA and NRDC's petition for a writ of mandamus.

February 2014 came and went, but the EPA did not take final action on the 2007 Petition. PANNA and NRDC

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[50] *Id.*

[51] *Id.*

[52] *Id.* at 17.

[53] *PANNA v. EPA* (*In re PANNA*), 532 F. App'x 649, 651 (9th Cir. 2013).

returned to this Court in September 2014 with a second petition for a writ of mandamus.

Shortly thereafter, in December 2014, the EPA published a Revised Human Health Risk Assessment. It expressed greater certainty both that chlorpyrifos was causing the neurotoxic harms seen in the cohort studies and that it was doing so through a mechanism other than AChE inhibition.[54]

Because the EPA concluded that chlorpyrifos could cause harm even if exposure was below the AChE inhibition-related point of departure, the EPA proposed a new method for calculating a point of departure. But with all this, the EPA still did not act on the 2007 Petition.

In August 2015, this Court therefore granted the second mandamus petition.[55] The EPA had offered an "ambiguous plan to possibly issue a proposed rule nearly nine years after receiving the administrative petition," and the Court found this to be "too little, too late."[56] The Court found the EPA's delay "egregious" and ordered the EPA "to issue a full and

[54] Memo from Danette Drew et al. to Tom Myers et al. re: Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, EPA (Dec. 29, 2014) (hereinafter "2014 Revised Human Health Risk Assessment"), at 43 ("[C]hlorpyrifos likely played a role in the neurodevelopmental outcomes observed in these epidemiology studies."); *id.* at 46 ("[The] EPA believes it is unlikely mothers enrolled in the [Human Cohort Studies] experienced [red blood cell] AChE inhibition"); *see also id.* ("Given the differences across laboratory animal and epidemiology studies, the qualitative similarity in research findings is striking.").

[55] *PANNA v. EPA* (*In re PANNA*), 798 F.3d 809, 811 (9th Cir. 2015).

[56] *Id.*

final response to the petition no later than October 31, 2015."[57]

E. 2015–2016: The EPA Finds That Chlorpyrifos Tolerances Are Unsafe

Once again, this Court's deadline came and went, and the EPA still did not take final action on the 2007 Petition. But in November 2015, the EPA published in the Federal Register a Notice of Proposed Rulemaking "proposing to revoke all tolerances for residues of the insecticide chlorpyrifos."[58] It wrote: "The agency is proposing to revoke all of these tolerances because [the] EPA cannot, at this time, determine that aggregate exposure to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe."[59] Specifically, the EPA found that "contributions to dietary exposures to chlorpyrifos from food and residential exposures are safe," but "when those exposures are combined with estimated exposures from drinking water, as required by the FFDCA, . . . safe levels of chlorpyrifos in the diet may be exceeded for people whose drinking water is derived from certain vulnerable watersheds throughout the United States."[60]

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[57] *Id.*

[58] Chlorpyrifos; Tolerance Revocations, 80 Fed. Reg. 69,080, 69,081 (Nov. 6, 2015) (hereinafter "2015 Notice of Proposed Rulemaking").

[59] *Id.*

[60] *Id.*

The EPA adhered to the findings of the 2014 Revised Human Health Risk Assessment. It relied upon "a considerable and still-growing body of literature on the effects of chlorpyrifos on the developing brain of laboratory animals (rats and mice) indicating that gestational and/or postnatal exposure may cause persistent behavioral effects into adulthood."[61] It also relied upon the three Human Cohort Studies:

> [The] EPA has considered the strengths and limitations of these studies, and believes that random or systematic errors in the design, conduct or analysis of these studies were unlikely to fully explain observed positive associations between *in utero* [organophosphate] exposure and adverse neurodevelopmental effects observed at birth and through childhood (age 7 years). [The] EPA believes these are strong studies which support a conclusion that [organophosphates] likely played a role in these outcomes.[62]

The EPA acknowledged "significant uncertainties . . . about the actual exposure levels experienced by mothers and infant participants in the three children's health cohorts," but found that the measured exposures "are likely low enough that they were unlikely to have resulted in AChE inhibition."[63]

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[61] *Id*. at 69,090.

[62] *Id*. at 69,091.

[63] *Id*. at 69,093.

Since, however, the proposed rule did not constitute a final response to the 2007 Petition, this Court, in December 2015, ordered the EPA "to take final action by December 30, 2016 on its proposed revocation rule and its final response to . . . [the] 2007 [P]etition."[64] In other words, this Court, despite the EPA's repeated disregard of this Court's orders, most leniently gave the EPA yet another year to rule on the 2007 Petition.

In April 2016, the EPA convened another SAP, which peer-reviewed the 2014 Revised Human Health Risk Assessment. The 2016 SAP "agree[d] that both epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures below levels that result in 10% red blood cell [AChE] inhibition."[65]

However, the 2016 SAP disagreed with the EPA's method for calculating a new point of departure. Specifically, "with the exception of one Panel member, the Panel stated that using [umbilical] cord blood chlorpyrifos concentrations for derivation of the [point of departure] could not be justified by any sound scientific evaluation."[66] "Many Panel members" also objected to the specific threshold of harm that the EPA used to replace 10% AChE inhibition – a 2% decline in working memory – saying that

[64] *PANNA v. EPA* (*In re PANNA*), 808 F.3d 402 (9th Cir. 2015).

[65] SAP Minutes No. 2016-01, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Chlorpyrifos: Analysis of Biomonitoring Data 18 (Apr. 19–21, 2016) (hereinafter "2016 SAP Minutes").

[66] *Id*. at 26.

such a change in working memory was "of questionable biological significance."[67]

On the other hand, the 2016 SAP explained that, in general, it "support[ed] the use of measured maternal chlorpyrifos blood concentrations as a surrogate for fetal exposure . . . ."[68] And the SAP offered some guidance on how to proceed. "Multiple panel members noted that [physiologically based pharmacokinetic ("PBPK")] modeling is a valuable tool,"[69] and the SAP recommended that the EPA "consider determination and characterization of time-weighted average blood concentrations for different exposure scenarios,"[70] rather than measurements based upon umbilical cord blood concentrations at a single point in time.

The EPA returned to this Court in June 2016, claiming that it once again could not meet the much-extended deadline for final action on the 2007 Petition. In August 2016, the Court denied the EPA's request for an additional six months.[71] The Court did, however, grant the EPA a three-month extension, to March 31, 2017. The Court acknowledged that "evidence may be imperfect . . . [,] the feasibility inquiry is formidable, and . . . premature rulemaking is undesirable," but the Court found that "at this stage, a claim of premature rulemaking has come and

[67] *Id*. at 27.

[68] *Id*. at 18.

[69] *Id.*

[70] *Id*. at 70.

[71] *NRDC v. EPA* (*In re PANNA*), 840 F.3d 1014, 1015 (9th Cir. 2016).

gone."[72] The Court warned that this was "the final extension" and that the Court would "not grant any further extensions."[73]

In November 2016, the EPA revised its Human Health Risk Assessment again. The 2016 Revised Human Health Risk Assessment remains the EPA's most recent comprehensive assessment of the risks of chlorpyrifos. In the assessment, the EPA "continue[d] to conclude that the [Human Cohort Studies] provide the most robust available epidemiological evidence."[74] The EPA "acknowledge[d] the lack of [an] established" mechanism of action that would explain the neurotoxic effects and also recognized "the inability to make strong causal linkages, and the unknown window(s) of susceptibility."[75] The EPA concluded, nevertheless, that "[t]hese uncertainties do not undermine or reduce the confidence in the findings of the epidemiology studies. The epidemiology studies . . . represent different investigators, locations, points in time, exposure assessment procedures, and outcome measurements."[76] "In summary," the EPA concluded that "the [Columbia Study], with supporting results from the other [two Human Cohort Studies] and the seven additional epidemiological studies

[72] *Id.* (quoting *Public Citizen Health Rsch. Grp. v. Chao*, 314 F.3d 143, 154–55 (3d Cir. 2002)).

[73] *Id.*

[74] Memo from Wade Britton to Dana Friedman re: Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review, EPA (Nov. 3, 2016) (hereinafter "2016 Revised Human Health Risk Assessment"), at 12.

[75] *Id.*

[76] *Id.*

reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition."[77] Based on this finding, the EPA continued to conclude that it was necessary to adopt an approach "protective of both the AChE inhibition and any adverse effects that could occur at lower doses."[78]

The EPA acknowledged that "the 2016 SAP did not support using the [Columbia Study] cord blood" to derive a new point of departure.[79] Responsive to those comments, the EPA adopted a different approach.[80] It accepted the 2016 SAP's statement that the "EPA should use estimated peak blood concentrations or [time-weighted average] blood concentrations within the prenatal period" rather than umbilical cord blood concentrations at the time of delivery.[81] Also, consistent with the 2016 SAP's comments, the EPA

[77] *Id*. at 13.

[78] *Id.*

[79] *Id.*

[80] *Id.* at 4 ("Given that the window(s) of susceptibility are currently not known for the observed neurodevelopmental effects, and the uncertainties associated with quantitatively interpreting the [Columbia Study] cord blood data, the SAP recommended that the agency use a time weighted average . . . blood concentration of chlorpyrifos for the [Columbia] [S]tudy cohort as the [point of departure] for risk assessment. [The] EPA has chosen to follow that advice in this assessment.").

[81] *Id*. at 14.

estimated blood concentrations using a PBPK model devised by a chlorpyrifos registrant.[82]

When the EPA compared the resulting safety thresholds against typical pesticide exposure scenarios, it determined that chlorpyrifos tolerances were not safe – even considering food alone, without aggregating other exposure sources, like drinking water.[83] For example, the EPA found that expected food exposure for children 1–2 years of age was 14,000% of the threshold level of risk concern.[84]

The EPA announced the findings of the 2016 Revised Human Health Risk Assessment through a Notice of Data Availability published in the Federal Register,[85] and it reopened the comment period on its 2015 Notice of Proposed Rulemaking. In the Notice of Data Availability, the EPA reiterated that the present tolerances are "not

[82] *Id.*

[83] *Id.* at 24.

[84] *Id*. at 6.

[85] 2016 Notice of Data Availability, *supra* note 3, 81 Fed. Reg. at 81,050 ("After careful consideration of public comments and the SAP's recommendations, [the] EPA has concluded the most appropriate path for reconciling the SAP's concerns is to follow through on the SAP's recommendation to use a time weighted average approach. The agency agrees with the 2016 FIFRA SAP (and previous SAPs) that there is a potential for neurodevelopmental effects associated with chlorpyrifos exposure to occur at levels below 10% RBC AChE inhibition, and that [the] EPA's existing point of departure (which is based on 10% AChE inhibition), is therefore not sufficiently health protective.").

sufficiently health protective."[86] The Agency explained that its

> revised analyses do not result in a change to the EPA's proposal to revoke all tolerances but it does modify the methods and risk assessment used to support that finding in accordance with the advice of the SAP. The revised analysis indicates that expected residues of chlorpyrifos on most individual food crops exceed the 'reasonable certainty of no harm' safety standard under the [FFDCA].

The EPA adhered to its proposal to revoke chlorpyrifos tolerances, rather than modify them, explaining that the "EPA has not identified a set of currently registered uses that meets the FFDCA safety standard because it is likely only a limited number of food uses alone, and in combination with predicted drinking water exposures, would meet the standard."[87] The EPA has never retracted the findings in its 2016 Revised Human Health Risk Assessment.[88]

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[86] *Id.*

[87] *Id.*

[88] Today, the EPA's website continues to warn about chlorpyrifos, citing the 2016 Revised Human Health Risk Assessment:

> What does [the] EPA's revised human health risk assessment show?
>
> This assessment shows dietary and drinking water risks for the current uses of chlorpyrifos. Based on

F. 2017–Present: The EPA Denies the 2007 Petition

Faced with this Court's statement that it would brook no further delays in the EPA's ruling on the 2007 Petition, the EPA finally in April 2017 ruled on the 2007 Petition. Notwithstanding the findings in its own 2016 Revised Human Health Risk Assessment, however, the EPA's order denying the 2007 Petition (the "2017 Order") stated that, "despite several years of study, the science addressing neurodevelopmental effects remains unresolved."[89] Therefore, the EPA concluded that "further evaluation of the science during the remaining time for completion of [FIFRA] 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."[90]

> current labeled uses, the revised analysis indicates that expected residues of chlorpyrifos on food crops exceed the safety standard under the [FFDCA]. In addition, the majority of estimated drinking water exposure from currently registered uses, including water exposure from non-food uses, continues to exceed safe levels . . . .

EPA, Revised Human Health Risk Assessment on Chlorpyrifos, *available at* https://www.epa.gov/ingredients-used-pesticide-products/revised-human-health-risk-assessment-chlorpyrifos (last accessed Apr. 17, 2021).

[89] 2017 Order, *supra* note 24, 82 Fed. Reg. at 16,583.

[90] *Id.*

The EPA further explained that it was denying the 2007 Petition only because this Court had ordered it to make a decision, but that

> [the] EPA has . . . concluded that it will not complete the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without first attempting to come to a clearer scientific resolution . . . . Because the [Ninth] Circuit's August 12, 2016 order has made clear, however, that further extensions to the March 31, 2017 deadline for responding to the Petition would not be granted, [the] EPA is today also denying all remaining petition claims.

PANNA, NRDC, and others objected to the EPA's denial of the 2007 Petition, both by filing objections with the EPA and by seeking relief from this Court. The Court denied mandamus relief on the ground that the EPA had "now complied with our orders" to issue a decision, and "substantive objections must first be made through the administrative process."[91]

But even though the statute required the EPA to rule on petitioners' objections "[a]s soon as practicable after receiving the arguments of the parties," 21 U.S.C. § 346a(g)(2)(C), and even though these objections were simply reiterations of the positions petitioners had consistently taken since 2007, the EPA had still not responded to petitioners' objections *14 months later*, when

[91] *PANNA v. EPA* (*In re PANNA*), 863 F.3d 1131, 1132 (9th Cir. 2017).

the Court heard oral argument on petitioners' petition for review of the 2017 Order.

The EPA objected to this Court's consideration of the merits of the decision on the ground that, until the EPA ruled on petitioners' administrative objections, this Court lacked jurisdiction. A panel of this Court concluded that "the EPA is engaging in yet more delay tactics to avoid our reaching the merits of . . . whether chlorpyrifos must be banned from use on food products because the EPA has not determined that there is a 'reasonable certainty' that no harm will result from its use, even under the established tolerances."[92] The panel held that, under these circumstances, the Court had jurisdiction and that, on the merits, "the EPA bears a continuing obligation to revoke tolerances that it can no longer find with a 'reasonable certainty' are safe," and because the Agency could not make such a finding, the tolerance must be revoked.[93] The panel vacated the 2017 Order and remanded to the EPA with instructions to revoke all chlorpyrifos tolerances within 60 days after issuance of the mandate.[94]

Subsequently, however, a majority of nonrecused active judges voted to rehear the case en banc. The en banc Court did not address the jurisdictional question, but instead issued a writ of mandamus requiring the EPA to rule on the objections to the 2017 Order within 90 days.[95] In July 2019,

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[92] *LULAC v. Wheeler*, 899 F.3d 814, 827 (9th Cir. 2018), *vacated on reh'g en banc*, 914 F.3d 1189 (9th Cir. 2019).

[93] *Id.* at 829.

[94] *Id.*

[95] *LULAC v. Wheeler*, 922 F.3d 443, 445 (9th Cir. 2019) (en banc).

the EPA issued a final order (the "2019 Order") denying petitioners' objections and thereby completing the administrative denial of the 2007 Petition. The 2019 Order again relied upon the need for greater scientific certainty, but went further and held that "the objections and the underlying Petition are not supported by valid, complete, and reliable evidence sufficient to meet the Petitioners' burden under the FFDCA, as set forth in [the] EPA's implementing regulations."[96]

With the Court's jurisdiction now clear, petitioners petitioned for review of the 2017 and 2019 Orders. Several states moved to intervene. The en banc Court granted the motion to intervene, consolidated the cases, and returned the matter to this panel as a "comeback case."[97]

STANDARD OF REVIEW

The Administrative Procedure Act ("APA") authorizes the Court to "hold unlawful and set aside agency action, findings, and conclusions" if they are "arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,"[98] and to "compel agency action unlawfully withheld or unreasonably delayed."[99] Agency action is arbitrary and capricious where the agency has "offered an explanation for

[96] Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order, 84 Fed. Reg. 35,555, 35,557 (July 24, 2019) (hereinafter "2019 Order").

[97] *LULAC v. Wheeler*, 940 F.3d 1126, 1126–27 (9th Cir. 2019) (en banc); *see* 9th Cir. Gen. Order 3.6(b).

[98] 5 U.S.C. § 706(2)(A).

[99] *Id.* § 706(1).

its decision that runs counter to the evidence before the agency."[100]

ANALYSIS

I. Merits

The Court first considers whether the EPA lawfully denied the 2007 Petition. Petitioners argue that the EPA's 2017 and 2019 Orders were *ultra vires* under the FFDCA and arbitrary and capricious under the APA.

A. Whether the EPA Left in Effect a Tolerance Without Determining That It Is Safe

As noted above, the FFDCA provides that the EPA "may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe."[101] The statute also specifically requires that the EPA "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue" and "publish a specific determination regarding the safety of the pesticide chemical residue for infants and children."[102]

Courts "normally interpret[] a statute in accord with the ordinary public meaning of its terms at the time of its

[100] *Motor Vehicle Mfrs. Ass'n of the U.S., Inc. v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983).

[101] 21 U.S.C. § 346a(b)(2)(A)(i).

[102] *Id.* § 346a(b)(2)(C)(ii)(I)–(II).

enactment."[103] Furthermore, the FFDCA must be "given a liberal construction consistent with the Act's overriding purpose to protect the public health."[104]

The EPA admits that the 2017 and 2019 Orders left in effect tolerances without determining that they are safe, claiming that it could delay this determination for several more years until it had resolved safety-related issues in the 15-year FIFRA registration review. Since, as discussed below, the EPA's duty to engage in a periodic FIFRA registration review is separate from its continuous obligation to ensure safety under the FFDCA, this concession is effectively dispositive in favor of petitioners.

FIFRA aside, the EPA argues that it may leave in effect tolerances, without a new safety finding, "when [the] EPA concludes the petition contains insufficient evidence for [the] EPA to undertake proceedings to revoke or modify tolerances." This argument fails for two reasons. First, once the EPA has become aware, through a petition or otherwise, of genuine questions about the safety of an existing tolerance, the EPA has its own continuing duty under the FFDCA to determine whether a tolerance that was once thought to be safe still is, and here the EPA's own studies and pronouncements still in effect show that it regards chlorpyrifos as harmful at levels below the existing tolerances. Second, in any case, the 2007 Petition, under the EPA's own regulations, contained more than sufficient evidence to undertake a safety review, and the EPA recognized as much, began such a review, and only now,

[103] *Bostock v. Clayton County*, 140 S. Ct. 1731, 1738 (2020).

[104] *United States v. An Article of Drug . . . Bacto-Unidisk*, 394 U.S. 784, 798 (1969).

13 years later, claims for the first time that the 2007 Petition was somehow inadequate.

1. The EPA's Duty to Ensure Human Safety

The FFDCA imposes a continuous duty upon the EPA by permitting it to "leave in effect" a tolerance "only" if it finds it is safe. To "leave" something in effect means "to cause or allow [it] to be or remain in a specified condition."[105] Denying the 2007 Petition caused the chlorpyrifos tolerances to remain in place; as the EPA itself wrote in its brief, it "le[ft] the existing tolerances in place pending . . . registration review." But in so doing, the EPA did not "determine[] that the tolerance is safe."[106] Rather, the EPA's own pronouncements show that it has already concluded that it can no longer be reasonably certain that chlorpyrifos is safe at current tolerances.

It should be noted in this respect that, because of the FQPA, assurance of safety for human health is the primary issue the EPA must consider. Before 1996, when Congress unanimously passed the FQPA, the EPA interpreted the FFDCA to permit the balancing of safety against other considerations, such as economic factors. Congress was

[105] Merriam Webster, "Leave," *available at* https://www.merriam-webster.com/dictionary/leave (last accessed Apr. 17, 2021). The Dissent quibbles with our use of the dictionary, arguing that the phrase "leave in effect" is unambiguous. But then the Dissent ascribes to that term a meaning of the Dissent's own creation: that the EPA leaves in effect a tolerance only when it conducts FIFRA registration review. The statute imposes no such limitation on the phrase.

[106] 21 U.S.C. § 346a(b)(2)(A)(i).

aware of this,[107] and the FQPA largely abrogated that approach.[108] Congress made the explicit decision to prioritize safety over all else. This makes the FFDCA a remedial statute, which, as noted, must be "given a liberal construction consistent with the Act's overriding purpose to protect the public health."[109] Reading the EPA's duty narrowly would undermine the statute's health-protective purpose.

The EPA argues that one of Congress's purposes was to provide the EPA with regulatory discretion. The EPA points to the fifteen-year registration review cycle under FIFRA[110] as evidence that "Congress recognized that [reregistration] would be a complex and potentially burdensome proceeding"; thus, by contrast, Congress must have intended "a different" – and less burdensome – obligation "[w]hen [the] EPA responds to a petition to revoke pesticide tolerances" under the FFDCA. This contention is unpersuasive because of the differences between FIFRA and

[107] H.R. Rep. No. 104-669, pt. 2, at 40 (1996) (noting that under the prior procedure for setting tolerances, the EPA was authorized to consider "factors including the necessity for production of an adequate, wholesome, and economical food supply").

[108] Notwithstanding the safety standard, in certain circumstances the EPA may leave a tolerance in effect if "[u]se of the pesticide chemical . . . is necessary to avoid a significant disruption in domestic production of an adequate, wholesome, and economical food supply." 21 U.S.C. § 346a(b)(2)(B)(iii)(II). However, this is permitted only where the risk of harm from a "nonthreshold effect," such as cancer, is not significantly greater than would be allowed for threshold effects. *See id.* § 346a(b)(2)(B)(iv). Nonthreshold effects are not at issue here.

[109] *Bacto-Unidisk*, 394 U.S. at 798.

[110] *See* 7 U.S.C. § 136a(g)(1)(A)(iii)–(iv).

the FFDCA. The statutes impose different duties that require different assessments. Under FIFRA, the EPA has a discretionary power to cancel registrations for a variety of reasons.[111] Specifically, FIFRA requires the EPA to balance several factors in determining whether a pesticide should be registered. For example, although FIFRA review includes an assessment of safety under the FFDCA,[112] it also requires a more general assessment of a pesticide's "economic, social, and environmental costs and benefits,"[113] including "the impact of [any proposed] action . . . on production and prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy."[114] Given these differences, Congress's decision to give the EPA discretion to set FIFRA priorities does not translate to the FFDCA. The EPA's obligations under the FFDCA are linked to a single issue, safety, but they are mandatory.[115] The whole point of the FQPA would be destroyed if the EPA could exercise unfettered discretion to defer safety considerations until it

[111] 7 U.S.C. § 136d(b).

[112] *See id.* § 136(bb). The Dissent accuses us of "repeatedly miss[ing] this point," Dissent, *infra*, at 83 n.6, but the fact that FIFRA reregistration review includes, as one component, an assessment of safety under the FFDCA does not gainsay the many *other* factors FIFRA review also encompasses. FIFRA's wider scope justifies that statute's periodic rereview timeline and the greater agency discretion that approach entails. By contrast, the FFDCA's singular focus on safety corresponds with the EPA's continuous duty to leave in effect a tolerance only if it finds that the tolerance is safe.

[113] 7 U.S.C. § 136(bb).

[114] *Id.* § 136d(b).

[115] *See* 21 U.S.C. § 346a(b)(2)(A)(i) ("The Administrator *shall* modify or revoke [an unsafe tolerance]." (emphasis added)).

was prepared to engage in the full multi-factor balancing assessment required for FIFRA registration.

Our dissenting colleague reaches a different conclusion regarding the EPA's obligations, or lack thereof, when confronted with a petition for revocation of tolerances. The Dissent focuses upon two sentences in the FFDCA:

> The Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe.[116]

We think that these two simple sentences are – with their emphasis on the word "only" – remarkably straightforward. As here explained, they mean that the EPA can lawfully deny the 2007 Petition and thereby "leave in effect" a tolerance "*only* if the Administrator determines that the tolerance is safe." The Dissent's more strained reading of these sentences is to the effect that there are three possible scenarios, one in which the EPA "determines that a tolerance is safe," one in which the EPA "determines it is not safe," and one in which the EPA is unwilling or unable to make a safety determination at this time. In this latter, middle world, the Dissent continues, the statute is silent as to the EPA's obligations, leaving the EPA with the discretion to leave in

[116] *Id.* The EPA and the Dissent also contend that our reading renders the second sentence superfluous, but it does not. The second sentence limits the EPA's discretion by explaining that when it finds that a tolerance is not safe, it may not, for example, convene a SAP or wait 15 years pending further research; its only options are to revoke or modify the tolerance.

effect a tolerance based on its *prior* safety finding (here, the 2006 safety finding).

One problem (among others) with the Dissent's imaginative reading is that other statutory provisions are not silent. The FFDCA imposes an overarching obligation that the EPA protect human safety, and particularly the safety of infants and children:

> In establishing, modifying, leaving in effect, or revoking a tolerance or exemption for a pesticide chemical residue, the Administrator shall assess the risk of the pesticide chemical residue . . . and shall ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure to the pesticide chemical residue.[117]

Congress has excluded the middle, not this Court. The EPA can only lawfully take agency action to establish or leave in effect a tolerance (*e.g.*, denying the 2007 Petition) if the EPA finds that the tolerance is safe.

2. The Burdens of Production and Persuasion

The EPA claims that the issue of safety as it bears on an existing tolerance need not be addressed unless a petitioner meets a threshold burden to come forward with evidence that the existing tolerance is unsafe. In this regard, the EPA points to the fact that the FFDCA gives the EPA the authority to "establish the requirements for information and

[117] 21 U.S.C. § 346a(b)(2)(C) (punctuation and section lettering omitted).

data to support a petition to modify or revoke a tolerance."[118] In a regulation promulgated pursuant to that authority, the EPA requires such a petition to "furnish reasonable grounds for the action sought."[119] Reasonable grounds "include . . . an assertion of facts (supported by data if available) showing . . . that new data are available as to toxicity of the chemical, or that experience with the application of the tolerance . . . may justify its modification or revocation."[120]

We do not doubt that the EPA has gatekeeping authority to reject a wholly frivolous petition – *i.e.*, a petition that fails even to "furnish reasonable grounds for the action sought" – without publishing a notice of its filing if the petition is deficient on its face, and in such circumstances we can assume the EPA need not address the concerns raised by the petition. But the record here unequivocally shows both that the 2007 Petition met all relevant requirements and that, in fact, it caused the EPA to re-evaluate the safety of the chlorpyrifos tolerances, thus triggering the EPA's duty to ensure a reasonable certainty of no harm.

The FFDCA requires the EPA to determine whether a petition satisfies the threshold requirements *prior* to publishing a notice of the filing of the petition.[121] Here, the EPA published a notice of the filing of the 2007 Petition in

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[118] 21 U.S.C. § 346a(d)(2)(B).

[119] 40 C.F.R. § 180.32(b).

[120] *Id.*

[121] *See* 21 U.S.C. § 346a(d)(3) ("A notice of the filing of a petition *that the Administrator determines has met the [data and information] requirements* . . . shall be published by the Administrator within 30 days after such determination." (emphasis added)).

October 2007,[122] thereby finding that it met the data and information requirements in the FFDCA and the EPA's regulations promulgated thereunder. The EPA cannot now be heard, more than a dozen years later, to claim that the petition did not, in fact, meet those threshold requirements.

Independently, even if the EPA had raised this issue thirteen years ago when the 2007 Petition was filed, the EPA offers no specific way in which the petition failed to comply with the EPA's technical requirements and no plausible argument for why the 2007 Petition does not contain "reasonable grounds" for revocation. The EPA points to the continued scientific uncertainty regarding how chlorpyrifos harms infants and children and the fact that the 2007 Petition did not attach complete underlying data for the studies that it cited. But the regulation does not say that the petition must *prove* that revocation is required; it requires only that the petition state "reasonable grounds" for revocation. And the grounds listed in the 2007 Petition meet any definition of "reasonable"; indeed, the EPA has implicitly acknowledged as much by reacting to the 2007 Petition with years of deliberation, hundreds of pages of analysis, several convenings of the SAP, and a Notice of Proposed Rulemaking and further Notice of Data Availability proposing to grant the requested relief, all substantially based on grounds cited in the 2007 Petition.

The Dissent contends that a petitioner who seeks revocation of a pesticide tolerance bears not only a burden of production, *i.e.*, to provide "reasonable grounds" for revocation, but also a burden of persuasion, *i.e.*, to offer valid, complete, and reliable data that affirmatively demonstrate that the tolerances are unsafe. However, as

[122] 72 Fed. Reg. 58,845 (Oct. 17, 2007).

previously explained, the Dissent's reading is inconsistent with the FQPA's health protective purpose and the FFDCA's overarching command that the EPA, whenever leaving in effect a tolerance, "assess the risk of the pesticide chemical residue . . . and . . . ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure . . . ."[123] The Dissent's reading is also inconsistent with the EPA's regulations, which only impose a burden of production on the petitioner.[124] Indeed, in its brief the EPA relies upon the burden-setting regulation that would apply if the EPA conducted an evidentiary hearing on the 2007 Petition. Although there was no evidentiary hearing here, the regulation is illustrative. Ordinarily, "[t]he party whose request for an evidentiary hearing was granted has the burden of going forward in the hearing with evidence as to the issues relevant to that request for a hearing."[125] However, when section 408 of the FFDCA is at issue, the section pertaining to "safety," then "[t]he party or parties who contend that a regulation satisfies the criteria of section 408 of the FFDCA has the burden of persuasion in the hearing on that issue, whether the proceeding concerns the establishment, modification, or revocation of a tolerance or exemption from the requirement for a tolerance."[126] Put simply, on the question of safety, while the burden of production is on the petitioners, the burden of persuasion always rests on the party claiming that a tolerance is safe. For these reasons, the Court concludes that when the EPA

[123] 21 U.S.C. § 346a(b)(2)(C).

[124] 40 C.F.R. § 180.32(b).

[125] 40 C.F.R. § 179.91(a).

[126] *Id.* § 179.91(b).

publishes a petition seeking revocation of a tolerance and later takes final action denying that petition, the EPA leaves that tolerance in effect. The EPA can only do so if it finds the tolerance to be safe for the general population and for infants and children.[127] Here, the EPA did not make such findings, so it acted directly contrary to the FFDCA.

B. Whether Denying the 2007 Petition Was Arbitrary and Capricious

Separately, in light of the present record and the EPA's assessment of that record, petitioners argue that, even if the FFDCA does not require a safety finding here (which we find it does), the EPA's denial of the 2007 Petition was arbitrary and capricious. The Court agrees.

An agency has a baseline obligation to "articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'"[128] The EPA has not done so because none of the reasons proffered in the 2017 and 2019 Orders provides "a satisfactory explanation for" denying the 2007 Petition.

The EPA has not retracted the 2016 Revised Human Health Risk Assessment indicating that chlorpyrifos is not safe at current tolerances and has not issued a new Human

[127] This is not to say, of course, that the EPA must perform a new Human Health Risk Assessment in response to every petition. The EPA might consider the issues raised by the petition alongside all the other evidence considered in its most recent safety determination and conclude that it need not conduct further review before reaffirming its prior findings.

[128] *Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43 (quoting *Burlington Truck Lines v. United States*, 371 U.S. 156, 168 (1962)).

Health Risk Assessment or SAP report since 2016. Rather, the 2017 Order denied the 2007 Petition on purely discretionary grounds, relying upon the EPA's purported authority to demand more study through at least 2022. After 13 years of delay, a desire for yet more delay does not rationally support denial of a petition that the EPA's own prior studies indicate raises a genuine issue of ongoing harm to infants and children.

The EPA asserted in the 2017 Order that it "may lawfully re-prioritize the registration review schedule developed by earlier [presidential] administrations."[129] In other words, more delay. Furthermore, while the EPA recognized that the 2007 Petition was filed under the FFDCA and raised arguments concerning human safety, the EPA found in its 2017 Order that it had to be permitted to synchronize its review of the petition with FIFRA registration review. To find otherwise "would effectively give petitioners under the FFDCA the authority to re-order scheduling decisions regarding the FIFRA registration review process that Congress has vested in the Administrator."[130]

But the FIFRA registration review, as already noted, is a different animal, in that it permits a balancing of multiple factors, whereas a FFDCA review is limited to the sole issue of safety but allows no balancing as far as that factor is concerned. Chlorpyrifos's wide use and the significance of this issue to the Administration are not valid legal considerations, as the EPA recognized in its 2017 Order.[131]

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[129] 2017 Order, *supra* note 24, 82 Fed. Reg. at 16,590.

[130] *Id.*

[131] *Id.*

As already noted, the FQPA amended the FFDCA to explicitly prohibit the EPA from balancing safety against other considerations, including economic or policy concerns, in most instances. Thus, the EPA's citation to these admittedly extralegal factors in its denial of the 2007 Petition is telling. It strongly suggests that the EPA's about-face in 2017 was motivated by factors unrelated to human safety, contrary to the FFDCA's commands.

The reference in the denial to the FIFRA 15-year period of review is, instead, nothing but a red herring, as the 2007 Petition does not concern FIFRA registration review. It concerns a petition under the FFDCA that contends that chlorpyrifos is unsafe. The EPA's position would largely strip FFDCA petitions of meaning, converting them into comments for the EPA to consider whenever it gets around to the next FIFRA registration review. The EPA offers no statutory support for this – because there is none. When, as here, a petitioner files a detailed petition identifying new evidence providing reasonable grounds to believe that exposure at less than a pesticide's current tolerances may be unsafe, the EPA has a duty to "giv[e] due consideration to [the] petition . . . and any other information available"[132] and to act on that petition with reasonable dispatch to protect human health – not fifteen years later. For these reasons, consistent with what this Court has said for years, the EPA's desire for delay is not a satisfactory explanation for denying the 2007 Petition.

The 2019 Order (unlike the 2017 Order) relied upon a second ground for denial of the 2007 Petition. The EPA found that PANNA and the NRDC bore an initial burden of production that, according to the EPA, they did not meet.

[132] 21 U.S.C. § 346a(d)(4)(A).

The EPA pointed out that the FFDCA requires it to consider "the validity, completeness, and reliability of the available data"[133] and authorizes it to promulgate regulations stating what a petition must contain.[134] As noted above, under this authority, the EPA promulgated a regulation requiring a petition to include "reasonable grounds" for revocation, which include an "assertion of facts (supported by data if available)."[135] Given this initial burden of production, the "EPA conclude[d] that the information . . . presented by Petitioners is not sufficiently valid, complete, and reliable to support abandoning the use of AChE inhibition as the critical effect for regulatory purposes under the FFDCA section 408."[136] Thus, the EPA concluded that the FFDCA safety issue was not before it.

For reasons already stated, this finding is unreasonable and inconsistent with the petition itself. The 2007 Petition claimed in detail that chlorpyrifos posed a risk of neurotoxic harm, especially to infants and children, and it invoked the live animal studies and the Columbia Study as evidence. The EPA acknowledges that it "has, since [2006], consistently concluded that the available data support a conclusion of increased sensitivity of the young to the neurotoxic effects of chlorpyrifos and for the susceptibility of the developing brain to chlorpyrifos."[137] Therefore, under any reasonable construction, the 2007 Petition met the low

[133] 21 U.S.C. § 346a(b)(2)(D)(i).

[134] *Id.* § 346a(d)(2)(B).

[135] 40 C.F.R. § 180.32.

[136] 2019 Order, *supra* note 96, 84 Fed. Reg. at 35,563.

[137] *Id.*

bar of stating "reasonable grounds" for revocation with an "assertion of facts" in support. Also, as noted above, the time for finding that the petition did not meet the burden of production was in 2007, *before* the EPA published the petition in the Federal Register.

Because the Court rejects both of the EPA's justifications for refusing to make a safety finding, the Court concludes that the EPA's denial of the 2007 Petition was arbitrary and capricious.[138]

Although not necessary for this determination, the Court, for completeness, also considers the EPA's four objections to the data.

First, the EPA objects, in general, that "the science on this question is not resolved and would benefit from additional inquiry."[139] It will always be possible to conduct additional studies or to reach a greater degree of certainty, but a generalized concern that the science is not resolved is not a rationale sufficient to support denying a revocation petition. The FFDCA requires that the EPA make a safety determination based on whatever "information" is

[138] The Dissent takes great umbrage at this conclusion, reminding us that "[w]hen an agency makes determinations 'within its area of special expertise, at the frontiers of science . . . a reviewing court must generally be at its most deferential.'" Dissent, *infra*, at 109 (alteration in original) (quoting *Balt. Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983)). If the 2019 Order had found that existing chlorpyrifos tolerances were safe, then such deference would be appropriate. But no such finding was made. It is the Order's utter *failure* to make a required safety determination that this Court finds was arbitrary and capricious. This has nothing to do with deference or non-deference to expertise and everything to do with simple compliance with the law.

[139] *Id*. at 35,560.

"available."[140] And, as this Court has said before, a statutory mandate to rely on "available" scientific data "does not mean 'the best scientific data possible.'"[141]

Second, the EPA argues that it does not know *how* chlorpyrifos's neurotoxic effects harm infants and children. But that is not the question before the EPA. The question is *whether* chlorpyrifos causes such harms. Even if the mechanism is unknown, if a tolerance is unsafe, then the EPA must revoke it.[142]

Third, the EPA argues that the studies of rats and mice applied a "dosing regimen . . . that differs from internationally accepted protocols."[143] The EPA says:

> [T]he in vivo laboratory animal studies generally use fewer days of dosing that are aimed at specific periods of rodent fetal or early post-natal development compared to internationally adopted guideline studies which are intended to cover both pre- and post-gestational periods. The degree to which these shorter dosing periods coincide

[140] 21 U.S.C. § 346a(d)(4)(A).

[141] *San Luis & Delta-Mendota Water Auth. v. Jewell*, 747 F.3d 581, 602 (9th Cir. 2014) (quoting *Building Indus. Ass'n v. Norton*, 247 F.3d 1241, 1246 (D.C. Cir. 2001)).

[142] *Cf. Am. Trucking Ass'ns, Inc. v. EPA*, 175 F.3d 1027, 1055 (D.C. Cir. 1999) (finding the EPA was not required to prove "how particles actually interact with cells and organs to cause sickness and death"), *aff'd in part and rev'd in part on other grounds sub nom. Whitman v. Am. Trucking Assn's*, 531 U.S. 457 (2001).

[143] 2019 Order, *supra* note 96, 84 Fed. Reg. at 35,563.

> with comparable windows of susceptibility in human brain development is unclear.[144]

This argument, apparently raised for the first time in the 2019 Order, is stated in cursory fashion. The EPA does not identify these "internationally accepted protocols" or explain why the EPA did not find deviations from these protocols to be troubling in the 2015 Notice of Proposed Rulemaking, the 2016 Notice of Data Availability, the 2016 Revised Human Health Risk Assessment, or the many other publications by the EPA that relied upon the animal studies. In any event, however, even if the Court were convinced, for the sake of argument, that divergence from these internationally accepted dosing protocols might somewhat diminish the value of these studies, it would not change the result, for reasons described below.

Fourth and finally, the EPA objects that it has been unable to get the raw data, as well as information concerning how residential pesticides were applied, from the Columbia Study. (Columbia, for its part, has expressed reasonable concerns about the subjects' privacy, especially given that the study covered a small geographic radius. Nevertheless, Columbia suggested to the EPA that it could make at least

[144] *Id*. The EPA also explains that "except for some studies conducted recently, most of the in vivo laboratory studies use doses that are higher than doses that cause 10% [red blood cell] AChE inhibition. These studies are therefore are [sic] not useful quantitatively to evaluate whether [the] EPA's current regulatory standard is or is not sufficient to preclude the potential for neurodevelopmental effects." *Id.* This objection is, of course, valid as far as it goes: studies that apply pesticide at doses above the current tolerance are less helpful in showing whether the tolerance is safe. But the EPA concedes that "some studies" use lower doses. The EPA offers no justification for refusing to consider these studies.

some of the datasets available for viewing in a secure data center.[145]) The EPA has changed its position over time regarding the value of this data. It initially requested the data, but after meeting with the Columbia researchers in 2014, the EPA abandoned its request for this data.[146] Later, when the EPA sought to develop a point of departure based upon the umbilical cord blood measurements in the Columbia Study, it sought the data again. However, the 2016 SAP took issue with an approach based upon those cord blood measurements, so, as explained above, the EPA moved to a time-weighted average approach based upon a registrant's PBPK model. As a result, the EPA once again determined that it did not need the Columbia data, explaining that its new approach "does not directly rely on quantitative measures of chlorpyrifos in cord blood obtained from [Columbia], and thus, the lack of access to the raw data from [Columbia] is less of an uncertainty."[147] The EPA has now reversed position yet again, reiterating its desire for the data.

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[145] *See* Chlorpyrifos Epidemiology Study Data De-identification Discussion (July 31, 2018).

[146] 2014 Revised Human Health Risk Assessment, *supra* note 54, at 391 ("As a result of this meeting and additional discussions with [Columbia] staff, [the] EPA concluded that access to the raw data would either not provide answers to [the] EPA's questions or that the information [the] EPA sought could be obtained without analyzing the raw data. Indeed, based on discussions in that meeting as well as further work conducted by agency staff, [the] EPA has gained additional information to better clarify and characterize the major issue areas identified as uncertainties. For these reasons, *[the] EPA decided that it would not further pursue its request for the analytic data file* from the [Columbia] researchers.") (emphasis added).

[147] 2016 Revised Human Health Risk Assessment, *supra* note 74, at 14.

The EPA's flip-flopping suggests the weakness of this objection. Nevertheless, even if the Court were to assume for the sake of argument that the underlying data, and information concerning the method of residential pesticide application, would be of some use and that the EPA's inability to access it might diminish the value of the Columbia Study, it would not change the result in this case.

This is because, while the EPA might reasonably conclude that divergences from international protocols and lack of access to raw data might affect the weight the EPA accords to these studies, they are nowhere near enough to show that the studies are entirely unreliable. The FFDCA requires the EPA to consider the "information" that is "available"[148] and to make a safety determination based on that information. In this case, live animal studies showing sex-linked, neurotoxic harms from *in utero* chlorpyrifos exposure are available – even if such studies are supposedly not perfectly aligned with (unspecified) international standards. And peer-reviewed cohort studies showing harms to infants' neurological development following their mothers' exposure to chlorpyrifos are available – even if the underlying data is not. The EPA speculates that it might find an error if the unspecified international standards were applied to the animal studies or if the data from the Human Cohort Studies were available. But that is all it is: speculation. Such speculation "runs counter to the evidence before the agency,"[149] so it cannot form the basis for denying the 2007 Petition.

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[148] 21 U.S.C. § 346a(d)(4)(A).

[149] *See Motor Vehicle Mfrs. Ass'n*, 463 U.S. at 43.

II. Remedy

The Court concludes that the EPA lacked power to deny the 2007 Petition without making the safety findings required by the FFDCA and that the EPA's decision was arbitrary and capricious. Therefore, the Court must, at least, "set aside the order or regulation complained of"[150] and remand to the EPA. Petitioners argue that the Court should also order the EPA to revoke the current chlorpyrifos tolerances and registrations by a date certain. Under the APA, the Court has the power to "compel agency action unlawfully withheld or unreasonably delayed."[151] The Court returns once more to the two sentences of the FFDCA that are key to assessing whether the Court should order the relief petitioners request:

> The Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe.[152]

The second sentence is more than a mere gloss on the first because the command inherent in the second sentence

[150] 21 U.S.C. § 346a(h)(2).

[151] 5 U.S.C. § 706(1).

[152] 21 U.S.C. § 346a(b)(2)(A)(i).

is important.[153] To be sure, the "only if" clause in the first sentence, standing alone, limits what the EPA may do when it determines that a tolerance is unsafe: it may not leave it in effect. But what are the EPA's options? May it order additional study? Convene another SAP? Wait for fifteen years to see if further evidence appears? No. The second sentence makes clear that, once the EPA has determined that a tolerance is not safe, it has no discretion to temporize pending additional research; it must modify or revoke the tolerance. For these reasons, if the EPA has determined that the present chlorpyrifos tolerances are not safe – or if that is the only conclusion the EPA could reasonably draw on this record – then the EPA has unlawfully withheld the relief that petitioners request.

On the present record, the only reasonable conclusion the EPA could draw is that the present tolerances are not safe within the meaning of the FFDCA. The EPA can find a tolerance safe only if there is "a reasonable certainty" of "no harm,"[154] and for nearly a decade, the EPA and its SAPs have concluded that there is *not* a reasonable certainty of no harm:

- **2012 SAP:** "[E]vidence suggest[s] that chlorpyrifos can affect neurodevelopment at levels lower than those associated with AChE inhibition, and that the use of AChE inhibition data may not be the most appropriate for dose-response modeling and

[153] For this reason, the EPA and the Dissent are also incorrect to contend that petitioners' reading of the statute contains surplusage. *See* Dissent, *infra*, at 80.

[154] 21 U.S.C. § 346a(b)(2)(A)(ii).

derivation of a point of departure for assessment of the neurodevelopmental risks of chlorpyrifos."[155]

- **2014 Revised Human Health Risk Assessment:** "[C]hlorpyrifos likely played a role in the neurodevelopmental outcomes observed in these epidemiology studies."[156] Moreover, "it is unlikely mothers enrolled in the [Human Cohort Studies] experienced [red blood cell] AChE inhibition."[157]

- **2015 Notice of Proposed Rulemaking:** "[The] EPA cannot, at this time, determine that aggregate exposure to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe."[158]

- **2016 SAP:** "[B]oth epidemiology and toxicology studies suggest there is evidence for adverse health outcomes associated with chlorpyrifos exposures

[155] 2012 SAP Minutes, *supra* note 48, at 53.

[156] SAP Minutes No. 2008-04, A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos 43 (Sept. 16–18, 2008).

[157] *Id.* at 46.

[158] 2015 Notice of Proposed Rulemaking, *supra*. note 58, 80 Fed. Reg. at 69,081.

below levels that result in 10% red blood cell [AChE] inhibition."[159]

- **2016 Revised Human Health Risk Assessment:** The Columbia Study, "with supporting results from the other [Human Cohort Studies] and the seven additional epidemiological studies reviewed in 2015, provides sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below that required for AChE inhibition."[160]

- **2016 Notice of Data Availability:** "[E]xpected residues of chlorpyrifos on most individual food crops exceed the 'reasonable certainty of no harm' safety standard under the [FFDCA] . . . . [The] EPA has not identified a set of currently registered uses that meets the FFDCA safety standard . . . ."[161]

Even in its brief here, the EPA, though it purports to withhold judgment on chlorpyrifos's safety, admits that it cannot conclude there is a reasonable certainty of no harm. Rather, the EPA represents that there are "*uncertainties* concerning the impact of chlorpyrifos on children" (emphasis added).

The EPA has not determined, and on this record reasonably could not determine to a "reasonable certainty"

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[159] 2016 SAP Minutes, *supra* note 65, at 18.

[160] 2016 Revised Human Health Risk Assessment, *supra* note 74, at 13.

[161] *Id.*

that aggregate chlorpyrifos exposures under the current tolerances pose no risk of harm. Therefore, by statutory definition, the present tolerances are not safe. Accordingly, the EPA's obligation is clear: it must modify or revoke chlorpyrifos tolerances and modify or cancel chlorpyrifos registrations.

The EPA cites cases counseling that upon reversal of agency action, an open-ended remand is the correct approach, "[g]enerally speaking"[162] and "except in rare circumstances."[163] But this is not a typical case. On the present record the EPA has limited legal discretion: its only options are to modify or revoke the tolerances. Nor would it be reasonable to remand for further factfinding after thirteen years of interminable delay. Indeed, further delay would make a mockery, not just of this Court's prior rulings and determinations, but of the rule of law itself. This is precisely the sort of "rare circumstance" where yet another open-ended remand would only frustrate the purpose of the FFDCA.

Finally, the EPA argues that "any order by this Court unilaterally ordering [the] EPA to revoke the existing tolerances for chlorpyrifos or cancel the existing registrations would raise serious due process concerns" for registrants and "violate Congress's procedures." Here, however, the Court is not unilaterally ordering the EPA to revoke existing tolerances; as explained below, it may instead modify such tolerances if it can make the requisite safety findings.

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[162] *INS v. Orlando Ventura*, 537 U.S. 12, 16 (2002).

[163] *Fla. Power & Light Co. v. Lorion*, 470 U.S. 729, 744 (1985).

In any event, remanding with specific instructions does not raise due process concerns. In responding to a petition, the FFDCA explicitly authorizes the EPA to "issue a final regulation modifying or revoking a tolerance . . . (*which final regulation shall be issued without further notice and without further period for public comment*)."[164] On this record, immediate issuance of a final regulation is the only reasonable action, and the Court orders the EPA to do so.

Such a final regulation could take one of two forms: either it could revoke all chlorpyrifos tolerances or it could modify chlorpyrifos tolerances *and* conclude that under the new tolerances there is a "reasonable certainty that no harm will result" due to "aggregate exposure to the pesticide chemical residue" that would result from such modified tolerances, including "to infants and children."[165] To be clear, the EPA may only choose to modify chlorpyrifos tolerances, rather than to revoke them, if at the same time it publishes such a safety determination.[166] On this record, it

[164] 21 U.S.C. § 346a(d)(4)(A)(i) (emphasis added) (comma omitted).

[165] *Id.* § 346a(b)(2)(A)(ii), (b)(2)(C)(ii)(I).

[166] The Dissent opines that the Court "may have effectively foreclosed other options Congress made available," Dissent, *infra*, at 112 n.11, such as the exceptional steps the EPA may take when "the residue protects consumers from adverse effects on health that would pose a greater risk than the dietary risk" or when the tolerance "is necessary to avoid a significant disruption in domestic production of an adequate, wholesome, and economical food supply." 21 U.S.C. § 346a(b)(2)(B)(iii). These provisions offer alternatives to the FFDCA's general safety requirement for certain "eligible pesticide chemical residues," but only for adults. While subparagraph (b)(2)(B) provides an exception to "subparagraph [(b)(2)(A)(i)]," the general safety rule, it expressly requires compliance with subsection (b)(2)(C), which

may well be that the EPA cannot make such a determination. In 2016, the EPA explained that it "ha[d] not identified a set of currently registered uses that meets the FFDCA safety standard,"[167] a finding consistent with more than a decade of EPA issue papers, revised human health risk assessments, and SAP proceedings.

Nevertheless, during the pendency of this proceeding, in December 2020, the EPA issued a Proposed Interim Registration Review Decision proposing to modify certain chlorpyrifos tolerances. The EPA also convened another SAP in 2020. If, based upon the EPA's further research the EPA can now conclude to a reasonable certainty that modified tolerances or registrations would be safe, then it may modify chlorpyrifos registrations rather than cancelling them.[168]

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mandates that the EPA assure a reasonable certainty of no harm to children specifically. *Id.* § 346a(b)(2)(B)(vi). Thus, these provisions are irrelevant because regardless of whether chlorpyrifos is an "eligible" pesticide for purposes of § 346a(b)(2)(B) – a question not briefed by the parties and raised sua sponte by the Dissent – the EPA may only leave in effect chlorpyrifos tolerances that are safe for children.

[167] 2016 Notice of Data Availability, *supra* note 3, 81 Fed. Reg. at 81,050.

[168] Whichever path the EPA chooses to take, the FFDCA also provides that within 60 days after the EPA publishes a final response to the 2007 Petition, either modifying chlorpyrifos tolerances and publishing a safety finding or revoking chlorpyrifos tolerances, anyone may object to the EPA's final order, 21 U.S.C. § 346a(g)(2)(A), and the EPA must then "issue an order stating the action taken" on those objections, *id.* § 346a(g)(2)(C). It is hard to imagine that registrants will have much to add, given the many opportunities they have already received to comment on the 2015 Notice of Proposed Rulemaking and the 2016 Notice of Data Availability, as well as to participate as *amici*

To be clear, however, this is not an open-ended remand or a remand for further factfinding. The EPA must act based upon the evidence and must immediately revoke or modify chlorpyrifos tolerances.

For these reasons, the Court remands this matter to the EPA with instructions to publish a legally sufficient final response to the 2007 Petition within 60 days of the issuance of the mandate. That response must be a final regulation that either revokes all chlorpyrifos tolerances or modifies chlorpyrifos tolerances *and* makes the requisite safety findings based on aggregate exposure, including with respect to infants and children.

While the Dissent effectively views this as a "tight deadline[],"[169] it agrees that the "EPA dithered far too long."[170] The EPA has had nearly 14 years to publish a legally sufficient response to the 2007 Petition. During that time, the EPA's egregious delay exposed a generation of American children to unsafe levels of chlorpyrifos. By remanding back to the EPA one last time, rather than compelling the immediate revocation of all chlorpyrifos tolerances, the Court is itself being more than tolerant. But the EPA's time is now up.

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curiae before this Court. But, in any event, registrants' 60-day period to object will follow the EPA's *final* revocation of chlorpyrifos tolerances (or modification with concomitant safety findings). If registrants ask the EPA to promulgate new chlorpyrifos tolerances or revert to higher tolerances, they must provide proof of safety, and the EPA can approve registrants' request only if the EPA concludes that there is a reasonable certainty of no harm, including for infants and children.

[169] Dissent, *infra*, at 115.

[170] Dissent, *infra*, at 67.

CONCLUSION

We **GRANT** the petitions for review. The 2017 Order and the 2019 Order are vacated, and the matter is remanded to the EPA, with instructions 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,"[171] including for "infants and children";[172] 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).

VACATED AND REMANDED, WITH INSTRUCTIONS.

BYBEE, Circuit Judge, dissenting:

This is a consequential proceeding. EPA has before it a petition to revoke the tolerances for chlorpyrifos, one of the most important pesticides in the United States. This is a very complicated statute and I agree with the majority that EPA dithered far too long before ruling on the petition. Beyond that, I disagree with the majority opinion and judgment. In

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[171] 21 U.S.C. § 346a(b)(2)(A)(ii).

[172] *Id.* § 346a(b)(2)(C)(ii)(I).

my view it has misread EPA's obligations to review pesticide chemical residue tolerances EPA has previously found to be "safe" under the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 346a(b)(2)(A)(i). Further, the majority has substituted its own judgment for EPA's decision and then concluded that, because there is a difference of opinion, EPA's decision must be arbitrary and capricious. *See* 5 U.S.C. § 706(2)(A). Difference is not caprice. Finally, among the options Congress entrusted to EPA when an existing tolerance is determined to be unsafe, the majority effectively mandates the option that EPA will enforce.

As to the first point, I part with the majority over EPA's duty with respect to the petition. According to the majority, EPA must find that chlorpyrifos is safe for human use, and EPA did not do so here. Maj. Op. at 41–46. EPA did find chlorpyrifos safe. That was the result of the proceedings in 2006, made final shortly before the present petition was filed. The question EPA had to answer in this proceeding is whether new scientific evidence is sufficient to require EPA to "modify or revoke" its prior determination. Under the FFDCA, EPA must do so "if the Administrator determines it is *not safe*." 21 U.S.C. § 346a(b)(2)(A)(i) (emphasis added). Because EPA found that chlorpyrifos was safe when it concluded its prior rulemaking in 2006, EPA properly determined here that there was insufficient evidence to conclude that chlorpyrifos is "not safe" and thus it was not required to "modify or revoke" those tolerances. EPA does not start from scratch when it is reviewing a petition to revoke or modify, but may rely on its prior finding. The majority would require, contrary to the FFDCA, that EPA start all over again. I take this point up in Part I.

As to the second point, the majority cherry-picks EPA's careful and honest questions about the safety of chlorpyrifos in light of various studies produced in the petition. Admittedly, it feels like EPA had this question under review for far too long—through three administrations—but the majority then assumes EPA's tentative conclusions are proven and concludes that it was arbitrary and capricious for EPA to determine otherwise. However, EPA never concluded that the studies presented to it were scientifically established. At every step of its overly cautious proceedings, EPA referred these studies to its Scientific Advisory Panel (SAP), which ultimately advised EPA that it could not verify the studies' conclusions. When EPA requested the underlying data, the studies' authors declined to produce it. Left without means of authenticating the studies, EPA concluded there was insufficient verifiable evidence to conclude that chlorpyrifos was "not safe" and to require EPA to modify or revoke its prior approval. The petition failed for lack of scientifically verifiable evidence. EPA explained all of this in detail, explained why it needed additional time to conduct the appropriate inquiries, and advised how it would proceed through the reregistration required by the statute. There is nothing arbitrary and capricious about that. I address this problem in Part II.

Not only do we decide that EPA's decision was arbitrary and capricious, but we have effectively decided the appropriate remedy. By ordering EPA either to revoke all tolerances or modify the tolerances with the requisite safety findings within 60 days, our order virtually guarantees the EPA will revoke chlorpyrifos tolerances. This is a vast overreach, a clear abuse of our discretion, as I discuss in Part III.

We can be unhappy with EPA's dilatory proceedings, but the remedy for that is a writ of mandamus, which we issued in *League of United Latin American Citizens v. Wheeler* (*LULAC III*), 922 F.3d 443 (9th Cir. 2019) (en banc). Now that EPA has complied fully with our directions, we don't get to set aside EPA's decision "simply because [we are] unhappy with the result reached." *Vt. Yankee Nuclear Power Corp. v. NRDC*, 435 U.S. 519, 558 (1978). Nor do we get to "second-guess[] the [agency's] weighing of risks and benefits." *Dep't of Com. v. New York*, 139 S. Ct. 2551, 2571 (2019). "[A] reviewing court must remember that" when an agency is acting "within its area of special expertise, at the frontiers of science," we "must generally be at [our] most deferential." *Balt. Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983). I respectfully dissent.

I

For starters, I fundamentally disagree with the majority over its construction of the FFDCA. The majority reads § 346a(b)(2)(A)(i), which is the critical section of the FFDCA for setting standards for pesticide use, as creating a binary choice for EPA: either a tolerance is "safe" or it is "not safe." The majority concludes that because EPA did not conclude that the chlorpyrifos tolerances were "safe" when it denied the petition, EPA must have concluded that they were "not safe" and the petition should have been granted. *See* Maj. Op. at 41 (EPA "left in effect tolerances without determining that they are safe . . . ."). With respect, the majority has misread the statute and its logic. I will start with some background on the statutes, then turn to how the majority has misread the statute, and conclude by addressing two additional arguments the majority makes.

A

Let's start with some background. EPA regulates pesticides pursuant to two statutes: the Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. § 346a, and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136a–136y. The provisions relevant here were adopted as amendments to those Acts in the Food Quality Protection Act of 1996 (FQPA), Pub. L. No. 104-170, 110 Stat. 1489 (Aug. 3, 1996). *See Nw. Coal. for Alts. to Pesticides v. EPA*, 544 F.3d 1043, 1046 (9th Cir. 2008). The FFDCA authorizes EPA to regulate pesticides used on food that pose safety risks to humans and to establish pesticide tolerance levels "necessary for the protection of public health." 21 U.S.C. § 346. FIFRA authorizes EPA to "limit the distribution, sale, or use" of pesticides "[t]o the extent necessary to prevent unreasonable adverse effects on the environment" and issue registrations for distribution or sale of pesticides. 7 U.S.C. § 136a(a).

The FFDCA begins with a presumption that all "pesticide chemical residue in or on a food . . . [is] unsafe." 21 U.S.C. § 346a(a)(1)(A). If the EPA Administrator determines that a pesticide is "safe," the Administrator may establish a regulatory "tolerance."[1] A pesticide may be deemed "safe" if EPA has found "that there is a reasonable

[1] EPA may also exempt a pesticide from the FFDCA, where either (1) use of the pesticide protects consumers from greater adverse health effects than the dietary risk of the pesticide or (2) the pesticide is necessary to avoid significant disruption in the food supply chain, so long as aggregate risk is not too high. 21 U.S.C. § 346a(b)(2)(B)(ii)–(iv).

Although some of the statutes I will cite here refer to exemptions, EPA did not consider exemption of chlorpyrifos in this proceeding.

certainty that no harm will result from aggregate exposure to the pesticide." *Id.* § 346a(b)(2)(A)(i), (ii). The FFDCA has a separate requirement protecting infants and children. EPA must separately assess the risk of the pesticide based on available information concerning consumption patterns, special susceptibility, and cumulative effects unique to infants and children. *Id.* § 346a(b)(2)(C)(i). Based on this assessment, EPA must "ensure that there is a reasonable certainty that no harm will result to infants and children from aggregate exposure" and "publish a specific determination regarding safety" of the pesticide for infants and children. *Id.* § 346a(b)(2)(C)(ii). In making these determinations, EPA "shall consider . . . the validity, completeness, and reliability of the available data" and "available information concerning the relationship of the results of such studies to human risk." *Id.* § 346a(b)(2)(D)(i), (iii).

In addition to establishing safe tolerance levels for pesticides under the FFDCA, EPA regulates pesticides under FIFRA by issuing registrations required for distribution or sale. 7 U.S.C. § 136a(a). EPA may register a pesticide where, in addition to other requirements, "it will perform its intended function without unreasonable adverse effects on the environment" and "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment." *Id.* § 136a(c)(5)(C), (D). "Unreasonable adverse effects on the environment" are unreasonable risks to man or the environment, including "human dietary risk . . . inconsistent with the standard under section 346a of Title 21." *Id.* § 136(bb). Thus, FIFRA incorporates the FFDCA safety determination into its registration assessment.

At the time the FQPA was passed in 1996, there were a number of existing tolerances in effect. The use of

chlorpyrifos, for example, has been federally authorized since 1965. *See Chlorpyrifos; Final Order Denying Objections to March 2017 Petition Denial Order*, 84 Fed. Reg. 35,555, 35,558 (July 24, 2019) (*Final Order*). The FFDCA, as amended by the FQPA, provided that "[r]egulations that establish tolerances" issued on or before August 3, 1996, "shall remain in effect unless modified or revoked." 21 U.S.C. § 346a(j)(3). The Act also instructed EPA to "review tolerances and exemptions for pesticide chemical residues in effect on [August 2, 1996]," and to determine whether to leave in effect, "modify or revoke" those tolerances in accordance with the new standards. *Id.* § 346a(q)(1).[2] The FFDCA provided that EPA "shall . . . modify or revoke the tolerance or exemption if the tolerance or exemption does not meet such requirements." *Id.* The FFDCA further provided that at any time EPA could, on its own initiative, issue regulations "establishing, modifying, . . . or revoking a tolerance for a pesticide . . . ." *Id.* § 346a(e)(1)(A). Once a pesticide has been approved and registered, FIFRA requires EPA to reevaluate the registration within 15 years, in this case no later than October 2022. 7 U.S.C. § 136a(g)(1)(A)(iii), (iv). During FIFRA reregistration, EPA must decide whether to leave a tolerance in effect or revoke or modify it. *Id.* § 136a(g)(1)(A).

The general standards for establishing, leaving in effect, modifying, or revoking tolerances are found in § 346a(b)(2)(A)(i):

[2] The FQPA required EPA to review tolerances in existence in 1996 according to a priority schedule. 21 U.S.C. § 346a(q)(1), (2). EPA placed chlorpyrifos in its first priority group and completed its review in 2006. *Final Order*, 84 Fed. Reg. at 35,558.

> The Administrator may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if the Administrator determines that the tolerance is safe. The Administrator shall modify or revoke a tolerance if the Administrator determines it is not safe.

These sentences are awkwardly written. For readability we can transpose them as follows:

> Only if the Administrator determines that a tolerance for a pesticide chemical residue in or on a food is safe may the Administrator establish or leave in effect the tolerance.[3] If the Administrator determines a tolerance is not safe, the Administrator shall modify or revoke the tolerance.

These standards are consistent with the presumption against the use of pesticides in food. *If* EPA determines a pesticide is safe, *then* EPA *may* establish a new tolerance or leave in place a tolerance previously established. However, *if* EPA determines a tolerance is not safe, *then* EPA *shall* modify or revoke the tolerance. Establishing or leaving a tolerance in place is not mandatory, even if EPA determines that a pesticide is safe; but if EPA determines a tolerance is not safe, it must modify or revoke the tolerance.

[3] This sentence could also be written as "If the Administrator establishes or leaves in effect a tolerance, then he has determined that the tolerance is safe."

When acting on its own initiative or in response to a petition,[4] the FFDCA requires EPA to consider "the validity, completeness, and reliability of the available data from studies of the pesticide" as well as other available information concerning risks and effects. § 346a(b)(2)(D). The statute also authorizes EPA to adopt regulations governing "requirements for information and data to support a petition to modify or revoke a tolerance." § 346a(d)(1), (d)(2)(B). EPA has issued regulations establishing these requirements and mandating supporting data and studies. 40 C.F.R. § 180.32(b). A petition must be supported by "reasonable grounds for the action sought," including "an assertion of facts (supported by data if available)" that "may justify [the tolerance's] modification or revocation." *Id.* § 180.32(b). The regulations also specify the form and content required for a petition. *Id.* § 180.7(b). Under its regulations, EPA may deny a petition when it finds that a petition is not supported by "reasonable grounds" for revocation. *Id.* § 180.32(b).

B

Now to the majority's errors. The majority reads § 346a(b)(2)(A)(i) as creating a binary choice, an "either/or" scenario: either a tolerance is "safe" or it is "not safe." For the majority, there is no middle ground. *See* Maj. Op. at 13, ("If a tolerance is not safe—in other words, if the EPA cannot determine that there is a reasonable certainty of no harm across all sources of exposure for infants, children, and adults—then the EPA no longer has discretion."), 62–63

[4] The FFDCA provides a mechanism for interested persons to petition EPA to "propos[e] the issuance of a regulation establishing, modifying, or revoking a tolerance for a pesticide chemical residue in or on a food." *Id.* § 346a(d)(1)(A).

("EPA has not determined . . . that aggregate chlorpyrifos exposures under the current tolerances pose no risk of harm. Therefore, by statutory definition, the present tolerances are not safe."). The majority's logic is irrefutable because the statement is, of course, a tautology. But as a tautology it is not helpful, because it doesn't tell us anything about the actual state of affairs. As Ludwig Wittgenstein once commented, "I know nothing about the weather when I know that it rains or does not rain."[5] The problem with the majority's reasoning is, in a phrase, the fallacy of the excluded middle. *See Wall v. Mich. Rental*, 852 F.3d 492, 496 (6th Cir. 2017) ("[A] statement of two contradictory facts [is] a statement of nothing at all under a venerable principle of logic—the law of the excluded middle."); *Miller v. Henman*, 804 F.2d 421, 426 (7th Cir. 1986) (rejecting the "Law of the Excluded Middle" in favor of "a third alternative"). It is true that § 346a(b)(2)(A)(i) uses the terms "safe" and "not safe." But the context for the terms is different. The terms are opposites, but they do not exhaust the possible outcomes.

We should be familiar with the problem of the excluded middle from other areas of law and life. For example, "guilty" and "not guilty," as logical opposites, describe the universe, so long as we don't care about factual innocence. But if we do, we have to consider a third alternative. Thus, we have examples where courts have gone beyond the binary thinking of guilty/not guilty to declare persons "factually innocent." *See Humphries v. Cnty. of L.A.*, 554 F.3d 1170, 1181–82 & nn. 6, 8 (9th Cir. 2009) (discussing the legality and effect of findings of "factually innocent" by a California criminal court and "not true" by a California juvenile court

[5] Ludwig Wittgenstein, *Tractatus Logico-Philosophicus*, *quoted in* Joseph G. Brennan, *A Handbook of Logic* 160 (2d ed. 1961).

in a child abuse case), *rev'd in part on other grounds*, *Cnty. of L.A. v. Humphries*, 562 U.S. 29 (2010). Other countries offer juries the option of a third verdict. *See* Samuel L. Bray, Comment, *Not Proven: Introducing a Third Verdict*, 72 U. Chi. L. Rev. 1299, 1299–1300 (2005) ("Not proven and not guilty are both acquittals, indistinguishable in legal consequence but different in connotation. Not guilty is for a defendant the jury thinks is innocent; not proven, for a case with insufficient evidence of guilt"; citing Scottish law as an example). In football, a ruling may be overturned only if there is indisputable evidence that it was wrong. But what if the ruling is not indisputably wrong? Do we care if it was correct, or just "not wrong"? Turns out that we do. The presumption will lie with the official who made the call. If the ruling cannot be overturned, "the ruling on the field stands." But if the ruling on the field is correct, then "the ruling on the field is confirmed." *See NCAA Football Rules Book* R. 12, § 6, art. 1.d (2019) (distinguishing three options: "the ruling on the field is confirmed," "the ruling on the field stands," and reversing a ruling). There is no practical difference in the immediate effect on the game between "the ruling on the field stands" and "the ruling on the field is confirmed," but there are collateral consequences for officials and for the lively debates among the fans that inevitably follow in close games.

The majority's premise that a pesticide is either "safe" or "not safe" ignores an important alternative—namely, that there is insufficient information to reach either of those conclusions. That is why Congress instructed EPA to consider "the validity, completeness, and reliability of the available data"—it understood that the evidence might be inconclusive. 21 U.S.C. § 346a(b)(2)(D)(i). That is also why § 346a(b)(2)(A)(i) allocates a burden of persuasion. I hesitate to use the term "burden of proof" because it suggests

that EPA and petitioners are adverse to each other; they are not. EPA is responsible for regulating pesticide use and, as a court, we assume that it has developed an expertise. We also assume that EPA will be an honest broker in assessing the safety of a pesticide; after all, agency employees have to eat the same food we do. So instead of "burden of proof," I am going to use the term "risk of nonpersuasion."

Here is how the risk of nonpersuasion figures into the FFDCA. When EPA receives a petition, it has a duty of inquiry, but it is a different duty depending on whether the decision on the table is whether to *establish or leave in effect* a tolerance (the first sentence of § 346a(b)(2)(A)(i)) or to *modify or revoke* a tolerance (the second sentence in that subsection). EPA (or a petitioner) has the initial burden to show that a proposed tolerance can be safely established. If the proposal does not satisfy that standard, EPA cannot adopt the proposed tolerance. EPA has the same burden when it considers an existing tolerance for reregistration. Recall that when the FQPA was adopted in 1996, that Act tightened the standards for pesticides. Because EPA had approved pesticides in use, the FQPA required EPA to review and reregister all existing tolerances to determine whether to "leave in effect" those tolerances. 21 U.S.C. §§ 346a(j)(3), (q)(1). Additionally, the FQPA, amending FIFRA, mandated that following that reregistration, EPA must review existing tolerances no less frequently than every 15 years. 7 U.S.C. § 136a(a), (g)(1)(A)(iv). In these reregistration proceedings, EPA must conclude that the existing tolerance is "safe" before it can "leave [it] in effect." 21 U.S.C. § 346a(b)(2)(A)(i). What happens if the evidence is inconclusive? Since there is a presumption that all pesticides are "unsafe," *id*. § 346a(a)(1), the risk of nonpersuasion means that EPA must either approve the tolerance or exempt it under other provisions of the FFDCA,

see id. § 346a(a)(1)(A), (B). As I transposed § 346a(b)(2)(A)(i) for readability, "only if the Administrator determines that the tolerance is safe may [the Administrator] establish or leave in effect a tolerance."

By contrast, when a petitioner requests modification or revocation of an existing tolerance, the risk of nonpersuasion cuts in the opposite direction. EPA has previously found the tolerance to be "safe." If EPA subsequently determines that the pesticide is "not safe," then it must modify or revoke the tolerance. What happens if the evidence is inconclusive? The risk of nonpersuasion means that EPA may, but does not have to, modify or revoke the tolerance. Section 346a(b)(2)(A)(i) is clear (as I have revised it for readability): "If the Administrator determines a tolerance is not safe, the Administrator shall modify or revoke the tolerance." Accordingly, when a petitioner files an appropriate petition claiming that a tolerance is not safe, EPA assumes a duty of inquiry, but not a duty of declaring anew that the tolerance is "safe." Here is the crucial distinction: *determining that a tolerance is "not safe"* is not the same as *not determining that a tolerance is "safe."* The majority's either/or approach has excluded the middle. As the First Circuit explained, albeit in a different context:

> Confronted by such conflict a reasonable person investigates matters further; he receives assurances or clarification before relying. A reasonable person does not gamble with the law of the excluded middle, he suspends judgment until further evidence is obtained. Explicit conflict engenders doubt, and to rely on a statement the veracity of which one should doubt is unreasonable. The law does not supply epistemological

> insurance. Nor does it countenance reliance on one of a pair of contradictories simply because it facilitates the achievement of one's goal.

Trifiro v. Nw. York Life Ins. Co., 845 F.2d 30, 33–34 (1st Cir. 1988).

The majority's either/or treatment of § 346a(b)(2)(A)(i) has two important consequences. First, it effectively reads the second sentence of that subsection out of the statute because, in the majority's understanding, EPA always has the burden to show that a tolerance is "safe," which means that it is, by definition, not "not safe." Or, to put it another way, in the majority's view, if at any time EPA does not affirmatively declare that a tolerance is "safe," the tolerance is, again by definition, "not safe." Under the majority's reading, the second sentence of § 346a(b)(2)(A)(i) doesn't do any work because in order to determine that a tolerance is "not safe" EPA must decide that it is not "safe." In other words, for the majority, in every case EPA has a duty of reregistration. The reason the majority has committed this error of logic is that it fails to appreciate the different context for the two sentences in § 346(b)(2)(A)(i). In the first sentence, the presumption runs against the tolerance because EPA is required to establish or reregister ("leave in effect") the tolerance. In the second sentence, *EPA has already determined that the tolerance is "safe,"* so the question is whether there is enough evidence to show that it is "not safe." When EPA denies a petition for insufficient evidence, it may rely on its prior determination that the tolerance is "safe." The two sentences operate in different contexts.

Second, the majority's reading means that petitioners can seize control of the statutory schedule for reviewing existing

tolerances. Under the FQPA, EPA had to review all existing tolerances, such as chlorpyrifos, under the new standard. And it had to do so "as expeditiously as practicable," but no later than 2006. 21 U.S.C. § 346a(q)(1). This EPA did in 2006, leaving in effect the chlorpyrifos tolerance. Under the FIFRA and the FFDCA, EPA would have to reevaluate chlorpyrifos for reregistration no later than October 2022. *See* 7 U.S.C. § 136a(g)(1)(A)(iv); *Final Order*, 84 Fed. Reg. at 35,558. In the interim, any interested person may petition EPA to modify or revoke the tolerance. Under the majority's reading of the FFDCA, to respond to the petition, EPA must either reregister chlorpyrifos as "safe" or modify or revoke the tolerance—but in either case the petition has altered the statutory review process for chlorpyrifos. Since petitioners can file petitions at will, EPA has lost control over its docket, and the statutory schedule has been derailed. As EPA put it, if

> EPA were required to truncate its ongoing registration review process to make a new FFDCA safety finding every time it received a petition to modify or revoke tolerances, petitioners would effectively have the authority to re-order the Administrator's scheduling of registration review decisions under FIFRA and dictate the extent of inquiry EPA may put to a matter before reaching a resolution.

Final Order, 84 Fed. Reg. at 35,565.

C

Despite the (relative) clarity of these provisions, the majority makes two arguments to get around this reading of § 346a(b)(2)(A)(i). First, the majority holds that any time

EPA considers a petition to modify or revoke an existing tolerance (which is governed by the second sentence of § 346a(b)(2)(A)(i)), it is "leav[ing] in effect" the tolerance (which is governed by the first sentence). Maj. Op. at 41–42. It concludes that EPA has "a continuous duty" under the FFDCA "to 'leave in effect' a tolerance 'only' if it finds it is safe." *Id.* at 42. Second, the majority claims that once EPA accepted the petition, because it was not "wholly frivolous," EPA had an independent duty to determine whether chlorpyrifos is "safe" and cannot now claim that the petition was "somehow inadequate." *Id.* at 42, 47. Neither point withstands scrutiny.

The majority's focus on EPA "leaving in effect" the chlorpyrifos tolerance misconceives the proceedings. Under the FFDCA, any petitioner had the right to petition EPA to "establish[], modify[] or revok[e]" a tolerance. 21 U.S.C. § 346a(d)(1)(A). "Leave in effect" is not mentioned as an option in the petition subsection, and for good reason: "leave in effect" has a particular context and meaning in the FFDCA. As I have explained, prior to the adoption of the FQPA in 1996, which established the current statutory standards in the FFDCA, there were tolerances in place for pesticides such as chlorpyrifos. The FQPA imposed a duty and a schedule on EPA to review all existing tolerances and to decide whether to "leave in effect" those tolerances. 21 U.S.C. § 346a(q)(1). *See also id.* § 346a(l)(3)(B) (explaining if EPA suspends a tolerance it "shall not be considered to be in effect," but if the suspension is terminated, "leaving the registration of the pesticide for such use in effect," EPA must rescind the suspension). Because the prior tolerances were not established under the same standards demanded by the FFDCA, as amended by the FQPA, EPA had to determine afresh that the preexisting tolerances were "safe." With respect to that review, EPA

could "leave in effect a tolerance . . . only if the Administrator determines that the tolerance is safe." *Id.* § 346a(b)(2)(A)(i). Under FIFRA, EPA must also re-certify its tolerances no less than every 15 years and decide whether to leave a tolerance in effect or modify or revoke it. 7 U.S.C. § 136a(g)(1)(A).[6] The majority has conflated EPA's responsibility with respect to the preexisting tolerances with its responsibility when it reviews a petition.

The majority reaches its conclusion because it reads § 346a(b)(2)(A)(i) in isolation from the rest of the statute. That leads the majority to consider a dictionary definition of the phrase. Maj. Op. at 42. Dictionaries can be useful for understanding terms. Here, recurring to a dictionary is neither necessary nor useful, because the term "leave in effect" is not ambiguous when it is read in context with the remainder of the statute. *See Carson Harbor Vill., Ltd. v. Unocal Corp.*, 270 F.3d 863, 878 (9th Cir. 2001) (en banc)

[6] Contrary to the majority's statements, FIFRA incorporates the FFDCA's standards. *See* 7 U.S.C. § 136(bb) (referring to "the standard under Section 346a of Title 21"). As part of its reregistration requirements for licensing, FIFRA requires EPA to review its FFDCA standards no less than every 15 years. *See Final Order*, 84 Fed. Reg. at 35,557 ("In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions for pesticide uses that result in residues in or on food."). Because FIFRA requires periodic recertification under FFDCA, the FFDCA standard governs chlorpyrifos's use, independent of anything required for licensing under FIFRA. The majority repeatedly misses this point. *See* Maj. Op. at 43–44 ("[EPA's claim that reregistration is required by FIFRA] is unpersuasive because of the differences between FIFRA and the FFDCA. The statutes impose different duties that require different assessments."), 51 ("FIFRA registration review . . . is a different animal, in that it permits a balancing of multiple factors, whereas a FFDCA review is limited to the sole issue of safety . . . .").

("Where the language is plain and admits of no more than one meaning the duty of interpretation does not arise, and the rules which are to aid doubtful meanings need no discussion." (quoting *Caminetti v. United States*, 242 U.S. 470, 485 (1917)); *see also Hughes Aircraft Co. v. Jacobson*, 525 U.S. 432, 438 (1999) ("[W]here the statutory language provides a clear answer, [the inquiry] ends there . . . ."); *Robinson v. Shell Oil Co.*, 519 U.S. 337, 340 (1997) ("Our inquiry must cease if the statutory language is unambiguous and the statutory scheme is coherent and consistent." (internal quotation marks and citations omitted)); *United States v. Williams*, 659 F.3d 1223, 1225 (9th Cir. 2011) ("If the plain meaning of the statute is unambiguous, that meaning is controlling . . . ."). When the statute offers a definition of a term, the statutory definition—even if it is a functional usage—governs. *Carson Harbor Vill.*, 270 F.3d at 878 ("When a statute includes an explicit definition, however, we must follow that definition, even if it varies from that term's ordinary meaning." (quoting *Stenberg v. Carhart*, 530 U.S. 914, 942 (2000) (alteration omitted)); *see also United States v. Havelock*, 664 F.3d 1284, 1289 (9th Cir. 2012) (en banc) ("Statutory construction must begin with the language employed by Congress and the assumption that the ordinary meaning of that language accurately expresses the legislative purpose. That assumption, however, does not apply where Congress provides a statutory definition." (internal citations and quotation marks omitted)). The FFDCA, as amended by the FQPA, is quite clear that "leave in effect" refers to a particular kind of proceeding mandated by Congress.

That brings us to the majority's second point. The majority attempts to shift the risk of nonpersuasion through a contorted reading of EPA's regulations regarding the filing of a petition. According to the majority, EPA has a

"gatekeeping authority to reject a wholly frivolous petition." Maj. Op. at 47. But if EPA accepts a petition, it "trigger[s] the EPA's duty to ensure a reasonable certainty of no harm" by re-evaluating chlorpyrifos and, if it decides to "leave in effect" the tolerance, it must certify chlorpyrifos as "safe." *Id.* According to the majority, accepting a petition flips the risk of nonpersuasion. But EPA's regulations say nothing of the kind.

In an exercise of its "gatekeeping authority," EPA has adopted "Procedure for modifying and revoking tolerances or exemptions from tolerances." 40 C.F.R. § 180.32. That regulation provides in relevant part:

> Any person may file with the Administrator a petition proposing the issuance of a regulation modifying or revoking a tolerance or exemption from a tolerance for a pesticide chemical residue. The petition shall furnish reasonable grounds for the action sought. Reasonable grounds shall include . . . an assertion of facts (supported by data if available) showing that new uses for the pesticide chemical have been developed or old uses abandoned, that new data are available as to toxicity of the chemical, or that experience with the application of the tolerance or exemption from tolerance may justify its modification or revocation.

Id. § 180.32(b). There is not a word in the regulation that would affect the risk of nonpersuasion. The regulation requires little to be a qualifying petition: "reasonable grounds," including "an assertion of facts" which shall be "supported by data *if available*." *Id.* (emphasis added). That

is the most modest of rules. EPA will generously accept such petitions and consider them. Accepting a petition—which in the majority's phrase means that they are not "wholly frivolous"[7]—is the lowest of bars. This is as it should be. We want interested persons—"any person"—to be able to go to EPA and suggest that it take a second look at a tolerance for a pesticide going on our food. But the majority takes EPA's decision to accept the petition as nullifying EPA's prior decision to approve the tolerance; effectively, EPA must start all over again. That's not how administrative law usually works. Under the FFDCA, EPA must modify or revoke the tolerance if it is "not safe." The majority would require EPA to prove that the tolerance is "safe."

Although EPA's *Final Order* was overdue, there was nothing improper in its form. EPA denied the petition and instead relied upon its 2006 safety determination for chlorpyrifos tolerances because it found that the data and studies supporting the petition were "not sufficiently valid, complete, and reliable" to support revocation. *Final Order*, 84 Fed. Reg. at 35,562–63. In other words, the data supporting the petition was not sufficient to support a determination that chlorpyrifos tolerances are "not safe." 21 U.S.C. § 346a(b)(2)(A)(i).

The FFDCA does not require EPA to make a new safety determination in response to a petition supported solely by studies that EPA has already considered and found insufficient for revocation while conducting its FIFRA review. Here, EPA considered the petition's cited studies at multiple instances during its own review and found that they

[7] So far as I can tell, the phrase "wholly frivolous" belongs to the majority.

were not reliable enough to support revocation without more information. *See Final Order*, 84 Fed. Reg. at 35,563. The agency's determination that the petition did not present sufficiently valid, complete, or reliable information to support revocation is thus supported by the record. *See* § 346a(b)(2)(D). Because the 2007 petition did not present reasonable grounds for modification or revocation, EPA was entitled to rely upon its 2006 safety finding while it engaged in its FIFRA review of chlorpyrifos tolerances. The tolerance had already been deemed "safe," and the petition did not raise sufficient grounds to overcome that presumption.

Under a correct reading of the statute, and proper allocation of the risk of nonpersuasion, we should be reviewing EPA's determination that the petition, and the evidence it mustered, was insufficient to determine that the chlorpyrifos tolerance is "not safe." That is not the inquiry the majority conducts, so in Part II I will review the proceedings before EPA, as punctuated by our orders, and its *Final Order*, which is the only decision we have authority to review. 5 U.S.C. § 704.

II

EPA's denial of the 2007 petition was not arbitrary or capricious. The denial of the petition did not conflict with any final agency findings or conclusions and, to the contrary, was supported by the extensive record of EPA's concerns with the petition's supporting studies over the course of nearly a decade. The only final agency action in effect for chlorpyrifos tolerances is the 2006 safety determination, and EPA's denial of the petition comports with this determination.

I will begin with a brief review of EPA's 2006–17 proceedings, with some emphasis on the questions and qualifications EPA raised at each step of those proceedings. I will then turn to the *Final Order* and our review under the APA.

A

In 2006, pursuant to the FFDCA, EPA completed a tolerance reassessment of chlorpyrifos and found that chlorpyrifos was eligible for reregistration and met the standard of 21 U.S.C. § 346a(b)(2). EPA, Office of Prevention, Pesticides and Toxic Substances, *Memo to Jim Jones from Debra Edwards, Finalization of Interim Reregistration Eligibility Decisions and Interim Tolerance Reassessment and Risk Management Decisions for the Organophosphate Pesticides, and Completion of the Tolerance Reassessment and Reregistration Eligibility Process for the Organophosphate Pesticides* (July 31, 2006) (*2006 Reregistration Decision*); *see also Final Order*, 84 Fed. Reg. at 35,558. In doing so, EPA found that chlorpyrifos tolerances were safe and left them in effect.

1. The Petition is filed; EPA conducts various studies for reregistration

In September 2007, the Pesticide Action Network North America (PANNA) and the National Resources Defense Council (NRDC) filed a petition with EPA to revoke all tolerances for chlorpyrifos based on new studies purporting to show that current chlorpyrifos tolerances were not safe. *See Petition to Revoke All Tolerances and Cancel All Registrations for the Pesticide Chlorpyrifos; Notice of Availability*, 72 Fed. Reg. 58,845 (Oct, 17, 2007); *see also Final Order*, 84 Fed. Reg. at 35,556**.** Petitioners raised ten claims alleging numerous errors in the *2006 Reregistration*

Decision, including claims that EPA ignored or misinterpreted data.[8] EPA was able to resolve seven of the ten claims relatively quickly. In July 2012 and July 2014, EPA issued interim responses indicating its intent to deny all but the three claims at issue here (grounds 7–9 in the petition), and it informed Petitioners of its intent to finalize all interim conclusions (grounds 1–6, and 10) when it resolved the remaining three claims, a decision to which Petitioners did not object. *Final Order*, 84 Fed. Reg. at 35,556; *see also In re Pesticide Action Network North America* (*PANNA I*), 532 F. App'x 649 (9th Cir. 2013) (denying petition for mandamus). The three claims not addressed by EPA in those responses were interrelated and concerned the potential for chlorpyrifos exposure at current tolerance levels to cause neurodevelopmental effects in children. *Final Order*, 84 Fed. Reg. at 35,556. However, EPA did not give these claims short shrift. Instead, early in its review, in 2009, the agency found the issues raised important enough questions that they should be addressed as part of an accelerated reregistration review of chlorpyrifos. *Id.* at 35,556 (noting that these claims "raised novel, highly complex scientific issues" that should be addressed in EPA's

[8] Petitioners alleged that EPA: (1) "ignored genetic evidence of vulnerable populations"; (2) "needlessly delayed a decision regarding endocrine disrupting effects"; (3) "ignored data regarding cancer risks"; (4) "misrepresented risks and failed to apply FQPA 10X safety factor" in its 2006 cumulative risk assessment; (5) "over-relied on registrant data"; (6) "failed to properly address the exporting hazard in foreign countries from chlorpyrifos"; (7) "failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children"; (8) "disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages"; (9) "failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition"; and (10) "failed to incorporate inhalation routes of exposure." *Final Order*, 84 Fed. Reg. at 35,556.

expedited reregistration review). Despite its 2022 statutory deadline, EPA announced that it planned to prioritize review of chlorpyrifos and complete reevaluation by 2015, years ahead of schedule. *Id.* at 35,558. However, this review proved to be complex, particularly with regard to the potential human health risks and neurodevelopmental effects of chlorpyrifos tolerances. *Id.*

In the interim, EPA convened scientific panels to evaluate the evidence and published reports. In 2008, as part of its reregistration review, EPA published a Science Issue Paper addressing chlorpyrifos hazards. EPA, Office of Pesticide Programs, *Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization* (Aug. 21, 2008). The paper summarized "data relevant to infants, children, and pregnant women," interpreted this data, and suggested alternatives for updating the mechanism used to assess chlorpyrifos tolerance safety. *Id.* at 7. The paper "preliminarily concluded that chlorpyrifos likely played a role in" adverse health effects in children. *Id.* at 52**.** However, the paper specifically noted that there had not been "a full and complete risk assessment/characterization" of the human health risks of chlorpyrifos and that "the [EPA] has not developed any final conclusions regarding updates to the chlorpyrifos hazard assessment." *Id.* at 7.

Later that year, EPA convened a Science Advisory Panel (SAP or the Panel), a federal advisory committee "established under the provisions of FIFRA" that "serves as the [EPA's] primary scientific peer review mechanism" for pesticide matters, to peer review the paper. EPA, *SAP Minutes No. 2008-04: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: The Agency's Evaluation of the Toxicity Profile of Chlorpyrifos* 2 (Sept. 16–18, 2008). The SAP also

considered several new studies concerning the risk of chlorpyrifos to pregnant women and children. The SAP's evaluation noted that "Panel members were concerned that a high degree of uncertainty is evident in the available data . . . ." *Id.* at 10. First, the Panel expressed concerns about several laboratory studies involving live rodents and the meaning of phrases used and experimental methods employed, and concluded that this data was "insufficient." *Id.* at 11–12. The Panel also considered three epidemiology studies, referred to as the Mt. Sinai, CHAMACOS, and Columbia University studies. The Columbia Study, which assessed chlorpyrifos risk to pregnant women, infants, and children, commanded particular attention. *Id.* at 12. The Panel found defects in all three of the studies, including concerns that the Columbia Study—the most robust of the three—did not provide sufficient data to be the sole factor for risk assessment or modifying tolerances and produced uncertainty through its measurement method. *Id.* at 12–13, 32–35, 43–44. Although the SAP found that the studies "raise concerns," the SAP also agreed that the studies were inconclusive. *Id.* at 13–14. The SAP concluded that "chlorpyrifos could have contributed to the birth and neurodevelopmental outcomes" indicated in the studies, but "that due to their limitations, the epidemiological data currently available are useful primarily for hazard identification." *Id.* at 13.

In 2011, EPA published a Preliminary Human Health Risk Assessment (*PHHRA*) for chlorpyrifos as part of its forthcoming FIFRA review. EPA, Office of Chemical Safety & Pollution Prevention, *Chlorpyrifos: Preliminary Human Health Risk Assessment for Registration Review* 1–2 (June 30, 2011). This assessment again considered the laboratory and epidemiology studies evaluated by the 2008 SAP and similarly noted their limitations. *Id.* at 29–34. The

PHHRA also considered developments since the 2008 SAP, including new data and follow-up analysis on the Columbia Study that had been recommended by the Panel. *Id.* at 34. EPA came to no definitive conclusion in the *PHHRA*, instead stating that analyses were ongoing and the final assessment would

> be based on a full scientific weight of evidence approach that considers the best available science and integrates all key lines of evidence, from empirical animal toxicology to observational human epidemiology studies, in an integrated framework analysis and will transparently address and clearly characterize the strength of the evidence and areas of remaining uncertainty and variability.

Id. at 42.

In April 2012, EPA again convened the SAP to consider the health effects of chlorpyrifos. EPA, *SAP Minutes 2012-04: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding Chlorpyrifos Health Effects* (April 10–12, 2012). The SAP recognized "a growing body of literature with laboratory animals (rats and mice) indicating that gestational and/or early postnatal exposure to chlorpyrifos may cause persistent effects into adulthood" and epidemiology studies "that have reported associations with birth outcomes, childhood neurobehavioral and neurodevelopment outcomes." *Id.* at 10. In addition to nine new laboratory studies, the 2012 SAP reviewed the same laboratory studies evaluated by the 2008 SAP, again noting the laboratory studies' limitations and "recommend[ing] these experimental outcomes be

regarded as exploratory, and hypothesis-generating, as opposed to being evidence of toxicity." *Id.* at 15. However, the Panel found that, despite concerns about the studies, "the collective weight of evidence from these studies demonstrate that it is probable that there are significant long-term adverse effects from chlorpyrifos exposure." *Id.* at 16. The 2012 SAP likewise considered the same epidemiology studies analyzed by the 2008 SAP, recognizing their strengths and limitations. *Id.* at 17–18, 48–50. The Panel noted that the epidemiological studies indicated "that chlorpyrifos likely plays a role in impacting the neurodevelopmental outcomes examined in the three cohort studies" but proposed further study because "the data generated from these studies alone are not adequate enough" to make a definitive risk assessment. *Id.* at 18–19. The SAP advised EPA to "explore additional ways of using these studies" and conduct additional research. *Id.* at 19–20.

In December 2014, EPA published a Revised Human Health Risk Assessment (*2014 RHHRA*) for chlorpyrifos. EPA, Office of Chemical Safety & Pollution Prevention, *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review* (Dec. 29, 2014). This revised assessment incorporated comments on the preliminary assessment and included assessment of new data. *Id.* at 5. The *2014 RHHRA* found that data, including the laboratory and epidemiology studies, "indicate that chlorpyrifos likely played a role in the neurodevelopmental outcomes reported by the epidemiologic study (Columbia University) investigators" but that "uncertainties . . . preclude definitive causal inference." *Id.* at 6. Yet again, EPA noted that the studies reflected both strengths and "notable limitations." *Id.* at 43. In this assessment, EPA also revised its approach to calculating chlorpyrifos "points of departure," or the

ceiling for safe exposure to a pesticide based on these studies. *Id.* at 40, 62–70, 131.

In January 2015, EPA announced the availability of the *2014 RHHRA* and sought public comments on "the Agency's risk assessment methodologies and assumptions . . . [and] suggestions for mitigating any risks identified in the [*2014 RHHRA*]." *Chlorpyrifos Registration Review; Revised Human Health Risk Assessment; Notice of Availability*, 80 Fed. Reg. 1,909, 1,910 (Jan. 14, 2015). Additionally, in March 2015, EPA advised counsel for the petitioners by letter that it intended to deny the three unresolved claims in the 2007 Petition—the claims at issue in this appeal. EPA, Office of Chemical Safety & Pollution Prevention, *Re: Chlorpyrifos Petition Dated September 12, 2007; March 2015 Provisional Response* (Mar. 26, 2015). EPA incorporated its prior partial petition responses from 2012 and 2014, which denied seven of the ten claims raised in the petition. *Id.* With respect to the three remaining claims, which were those related to infants and children and based on the Columbia, Mount Sinai, and CHAMACOS studies, EPA advised counsel that "EPA does not believe the claims raised in your petition establish a basis to revoke all chlorpyrifos tolerances and cancel all chlorpyrifos registrations." *Id.* at 3. The letter noted that EPA had "risk concerns" with exposure to chlorpyrifos in drinking water, but it was seeking comment on its *2014 RHHRA* and would "take appropriate action under the FFDCA and/or FIFRA to ensure that exposures to chlorpyrifos are consistent with the requirements of those statutes." *Id.* at 3–4.

2. We issue mandamus; EPA proposes to revoke the tolerances

Six months later, in August 2015, we issued a writ of mandamus ordering EPA "to issue either a proposed or final

revocation rule or a full and final response to the administrative petition." *In re Pesticide Action Network North America* (*PANNA II*), 798 F.3d 809, 815 (9th Cir. 2015). In response, EPA issued a proposed rule to revoke all chlorpyrifos tolerances because "EPA cannot, at this time, determine that aggregate exposure to residues of chlorpyrifos, including all anticipated dietary exposures and all other non-occupational exposures for which there is reliable information, are safe." *Chlorpyrifos; Tolerance Revocations*, 80 Fed. Reg. 69,080, 69,080–81 (Nov. 6, 2015) (*2015 Proposed Rule*). EPA advised that it was issuing the proposed rulemaking because of our mandamus order and that the proposal was "in advance of [EPA] completing its refined drinking water assessment." *Id.* at 69,083. EPA explained that it "believe[d] that acute dietary risk from food only does not present a significant risk" and that "EPA would therefore not be proposing the revocation of chlorpyrifos if dietary exposures were confined to food." *Id.* at 69,096–97. The basis for the proposed revocation was instead new data indicating that "for some portions of the country, food exposures, when aggregated with residential exposures and potentially more significant drinking water exposures, do present a significant risk concern and support revocation of all chlorpyrifos tolerances." *Id.* at 69,097. At the same time, EPA stated that it had "insufficient time to address comments received on the [2014] RHHRA," and it would "update this action . . . as EPA completes additional work." *Id.* at 69,083. EPA also cautioned that its analysis was incomplete and that it might yet modify the proposed rule based on the completed analysis and comments. *Id.* We then ordered EPA to take final action on the proposed rule and on PANNA and NRDC's petition no later than December 30, 2016. *In re Pesticide Action Network North America* (*PANNA III*), 808 F.3d 402, 403 (9th Cir. 2015).

In March 2016, EPA published a new Chlorpyrifos Issue Paper and solicited comment from the SAP regarding changing points of departure based solely on neurodevelopmental effects measured by the Columbia Study. EPA, Office of Pesticide Programs, *Chlorpyrifos Issue Paper: Evaluation of Biomonitoring Data from Epidemiology Studies* 9 (Mar. 11, 2016) (*2016 Issue Paper*). At the time EPA had proposed to revoke chlorpyrifos tolerances, "EPA had not completed a refined drinking water assessment or additional analysis of the hazard from chlorpyrifos that was suggested by several commenters." EPA, Office of Chemical Safety & Pollution Prevention, *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review* 3 (Nov. 3, 2016) (*2016 RHHRA*). After engaging in additional research, EPA—in this Issue Paper—proposed using different "toxicological points of departure" based on data from the Columbia Study, and sought the advice of the 2016 SAP on this new approach. *2016 Issue Paper* at 9.

In April 2016, the SAP convened to review the Issue Paper. EPA, *SAP Minutes No. 2016-01: A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Chlorpyrifos: Analysis of Biomonitoring Data* (April 19–21, 2016) (*2016 SAP Minutes*). The SAP expressed significant disagreement with the substance of the paper, including a lack of confidence that the Columbia Study "c[ould] accurately be used" in determining new points of departure. *Id.* at 18. The panel "thought the quality of the [Columbia Study] data is hard to assess when raw analytical data have not been made available, and the study has not been reproduced." *Id.* The SAP noted that review of the raw data from the Columbia Study could resolve some uncertainty regarding the study's conclusions. *Id.* at 20.

By mid-2016, claiming "extraordinary circumstances," EPA requested a six month extension on our order of final action. *In re Pesticide Action Network North America* (*PANNA IV*), 840 F.3d 1014, 1015 (9th Cir. 2016). EPA advised us that it had "issued its proposed rule before completing two studies that may bear on the Agency's final rule." *Id.* at 1015. We characterized EPA's request as "another variation on a theme 'of partial reports, missed deadlines, and vague promises of future action.'" *Id.* (quoting *PANNA II*, 798 F.3d at 811). We denied EPA's request and ordered final action by March 31, 2017. *Id.*

In November 2016, EPA released yet another Revised Human Health Risk Assessment, responding to the 2016 SAP's concerns. EPA, Office of Chemical Safety & Pollution Prevention, *Chlorpyrifos: Revised Human Health Risk Assessment for Registration Review* (Nov. 3, 2016) (*2016 RHHRA*). EPA recounted that in 2013 it had sought the raw data used in the Columbia Study, and although the researchers would not agree to provide EPA with the data, EPA "gained valuable insight into the conduct of the study." *Id.* at 9–10. EPA concluded that the SAP had rejected both the approach in the *2015 Proposed Rule* and the new method based on the Columbia Study. *Id.* at 3. EPA agreed with the SAP that, despite uncertainties in the studies, there was "sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels" below the tolerances. *Id*. at 13. As a result, EPA proposed following the 2016 SAP's recommendation to use a hybrid point of departure, rather than relying solely on the data from the Columbia Study. *Id.* at 13–14.

Within two weeks of issuing the *2016 RHHRA*, EPA reopened the comment period on the *2015 Proposed Rule*. *Chlorpyrifos; Tolerance Revocations; Notice of Data*

Availability and Request for Comment, 81 Fed. Reg. 81,049 (Nov. 17, 2016) (*2016 Request for Comments*). EPA noted that it was not proposing "a change to the EPA's proposal to revoke all tolerances but it does modify the methods and risk assessment used to support that finding in accordance with the advice of the SAP." *Id.* at 81,050; *see also id.* ("[T]he agency's analysis provided in this notice continues to indicate that the risk from the potential aggregate exposure does not meet the FFDCA safety standard."). At the same time, EPA expressed frustration with the process, and advised that "the timing of EPA's issuance of the proposal was dictated" by our order in *PANNA II*. *Id*. EPA was clear that the basis for its proposed revocation depended on studies that were incomplete. It observed that EPA had completed a water assessment, but "[b]ecause of the court decision . . . EPA was not able to complete a more refined drinking water assessment for chlorpyrifos in advance of the proposed rule" and that with additional time it conducted the assessment to provide "a more tailored approach to risk mitigation." *Id.* at 81,051. EPA admitted that

> In the proposal, EPA proposed revoking all tolerances largely because the agency could not make a safety finding based on drinking water exposure in highly-vulnerable watersheds. EPA reasoned if it could better identify where such vulnerable areas might be, it could be possible for registrants to amend product labeling in ways that might make unnecessary some number of the proposed tolerance revocations.

Id. Importantly, EPA warned that its proposed course of conduct was not fixed:

> Since EPA is still in the process of deliberating the provisions of a final rule, EPA cannot definitively state whether this information will provide support for any provision of the final rule, or that the agency has determined that it is appropriate to rely on this information in developing the final rule.

Id.

3. EPA denies the petition; we issue mandamus

In April 2017, EPA reversed course, issuing a final response to the 2007 petition, which denied it in full. *Chlorpyrifos; Order Denying PANNA and NRDC's Petition to Revoke Tolerances*, 82 Fed. Reg. 16,581 (April 5, 2017) (*2017 Denial*). The order stated:

> Following a review of comments on both the November 2015 proposal and the November 2016 notice of data availability, EPA has concluded that, despite several years of study, the science addressing neurodevelopmental effects remains unresolved and 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. EPA has therefore concluded that it will not complete the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without

> first attempting to come to a clearer scientific resolution on those issues.

Id. at 16,583. EPA thus denied the petition without resolving all scientific uncertainty concerning the tolerances "[b]ecause the 9th Circuit's August 12, 2016 order has made clear, however, that further extensions to the March 31, 2017 deadline for responding to the Petition would not be granted." *Id.* (referring to *PANNA IV*, 840 F.3d at 1015). EPA explained that the comments received in response to the *2015 Proposed Rule* "suggest that there continue to be considerable areas of uncertainty with regard to what the epidemiology data show and deep disagreement over how those data should be considered in EPA's risk assessment." *Id.* at 16,590. It then explained why it was denying the petition, rather than continuing its prior course:

> As the 9th Circuit has made clear . . . EPA must provide a final response to the Petition by March 31, 2017, regardless of whether the science remains unsettled and irrespective of whatever options may exist for a more complete resolution of these issues . . . .
>
> Although past EPA administrations had chosen to attempt to complete [FIFRA] review several years in advance of the statutory deadline (and respond to the Petition on the same time frame), it has turned out that it is not possible to fully address these issues early in the registration review period . . . . Accordingly, EPA is denying these Petition claims and intends to complete a full and appropriate review of the neurodevelopmental data before either

> finalizing the [2015] proposed rule . . . or taking an alternative regulatory path.

Id. EPA concluded that "given the importance of this matter and the fact that critical questions remain regarding the significance of the data addressing neurodevelopmental effects, EPA believes there is good reason to extend the registration review of chlorpyrifos and therefore to deny the Petition." *Id.*

Various organizations petitioned our court for review of EPA's order. On review of EPA's *2017 Denial*, the panel ordered EPA to revoke the chlorpyrifos tolerances. *League of United Latin American Citizens v. Wheeler* (*LULAC I*), 899 F.3d 814, 829 (9th Cir. 2018). Judge Fernandez dissented on the grounds that the *2017 Denial* was not a final action. *Id.* at 830–32 (Fernandez, J., dissenting). We granted en banc review, vacated the panel opinion, and ordered EPA to issue a final order. *League of United Latin American Citizens v. Wheeler* (*LULAC II*), 922 F.3d 443, 445 (9th Cir. 2019) (en banc). EPA issued its *Final Order* in July 2019, and we referred the petition back to the three-judge panel. *League of United Latin American Citizens v. Wheeler* (*LULAC III*), 940 F.3d 1126, 1127 (9th Cir. 2019).

B

EPA's *Final Order* responded to the two objections raised in *LULAC I*: (1) that the "EPA has unlawfully left chlorpyrifos tolerances in place without making the safety finding required by the FFDCA"; and (2) that EPA must revoke the tolerances because it "has previously found that chlorpyrifos tolerances are unsafe and has not disavowed those findings." *Final Order*, 84 Fed. Reg. at 35,561.

1. Failure to find that chlorpyrifos is "safe"

EPA first addressed Petitioners' argument that EPA was required to make a new safety finding to deny the petition. EPA found that it was not required to make a new safety determination in response to every revocation petition, the FFDCA did not require revocation in the absence of a new safety determination for each petition, and *even if* a new safety determination was required, both the FFDCA and EPA implementing regulations "require petitioners seeking withdrawal of a tolerance to support this request with valid, complete and reliable data that set forth why the tolerances are unsafe." *Id.* at 35,562.

The agency found that petitioners had not met their burden of presenting evidence that the tolerances must be revoked because "the information yet presented by Petitioners is not sufficiently valid, complete, and reliable." *Id.* at 35,562–63. EPA had already considered, during its 2006 review, the laboratory and epidemiological studies cited by Petitioners and had "consistently concluded" these studies did not warrant revocation based on "an evaluation across multiples lines of evidence." *Id*. at 35,563. EPA determined these studies were deficient because they lacked a "mechanistic understanding for effects on the developing brain," which precluded EPA from having a "valid or reliable way[] to bridge the scientific interpretation" of the studies with chlorpyrifos; the dosing regimen of the in vivo studies presented problems for "quantitative interpretation and extrapolation of the results" because they did not align with "internationally accepted protocols"; and EPA had been unable to obtain the raw data underlying the epidemiological studies, despite numerous efforts, to allow for verification of validity and reliability as well as replication. *Id.* EPA candidly acknowledged that its conclusion was "at odds"

with its *2016 RHHRA* but ultimately asserted that it had "undertaken considerable efforts to assess the available chlorpyrifos data." *Id.* at 35,564; *see also id.* ("EPA acknowledges this conclusion differs from the position supported in the 2016 revised human health risk assessment."). The agency concluded that "the shortcomings of the data identified raise issues of validity, completeness and reliability under the FFDCA that direct against using the data for risk assessment at this time." *Id.*

EPA explained that a majority of the 2016 SAP had concluded that use of the scientific studies under review for developing points of departure "could not be justified by any sound scientific evaluation." *Id.* at 33,564. The SAP "expressed significant reservations" about using the studies as the sole source of revised points of departure and "noted the incompleteness of the information," including the "reproducibility" of the data. *Id.* EPA concluded that "[b]ased on the uncertainties identified by the 2016 SAP," the data were "not complete." *Id*. EPA further laid out its requests to obtain the raw data underlying the studies and "visit[] [to] Columbia University in an attempt to better understand their study results and what raw data exist." *Id.* at 33,565. Although the university initially had pledged to share its data, it failed to produce it, citing "privacy concerns." *Id.* As a result, "EPA cannot validate or confirm the data analysis performed, the degree to which the statistical methods employed were appropriate, or the extent to which (reasonable or minor) changes in assumptions may have changed any final results or conclusions." *Id.* As a consequence, EPA concluded petitioners had "failed to meet their initial burden of providing sufficiently valid, complete, and reliable evidence that neurodevelopmental effects may be occurring at levels below EPA's current regulatory standard." *Id*.

EPA further concluded that denying the 2007 petition was appropriate because the claims in the petition would be subject to FIFRA registration review, which is a "more up-to-date, thorough and methodical" review. *Id.* EPA reiterated its commitment to complete FIFRA and FFDCA review of chlorpyrifos tolerances in advance of the October 2022 deadline, anticipating some updates "by summer of 2020." *Id.* at 35,566.

2. EPA's prior finding that chlorpyrifos is "not safe"

EPA also addressed petitioners' objection that the agency had already found chlorpyrifos to be unsafe in its 2015 proposed tolerance revocation. *Id.* at 35,566. EPA, however, was quite clear that "EPA has not made any findings that chlorpyrifos tolerances are not safe." *Id.* EPA pointed out that its last final action regarding the safety of chlorpyrifos tolerances—and the only regulatory finding in effect—was its 2006 reregistration and safety determination. *Id.* The *2015 Proposed Rule* was not a final agency action, and "EPA made clear it was issuing the proposal because of" the Ninth Circuit's order, "without having resolved many of the issues critical to EPA's FFDCA determination and without having fully considered comments previously submitted to the Agency." *Id.* It was up to EPA to "choose to finalize, modify or withdraw the proposal based on the comments received." *Id.* Accordingly, its prior proposed findings were "not binding pronouncements." *Id.*

C

EPA's decision to deny the petition in its entirety in response to our writ of mandamus is entirely reasonable. We ordered EPA to grant or deny the petitions; EPA did as we ordered. It has explained why it did so and explained how it will proceed with the chlorpyrifos reregistration, in which it

will have to decide whether it is "safe." There is nothing arbitrary or capricious in EPA's decision.

Although petitioners can argue that the denial of the petition conflicts with EPA's prior proposal, the *2015 Proposed Rule* is just that—a *proposed* rule. *2015 Proposed Rule*, 80 Fed. Reg. at 69,083 ("EPA may update this [proposed rule] with new or modified analyses as EPA completes additional work after this proposal."). "Agencies are entitled to change their minds." *Defenders of Wildlife v. Zinke*, 856 F.3d 1248, 1262 (9th Cir. 2017) (citation omitted); *see also Nat'l Ass'n of Home Builders v. Defenders of Wildlife*, 551 U.S. 644, 658–59 (2007) ("[T]he only 'inconsistency' respondents can point to is the fact that the agencies changed their minds—something that, as long as the proper procedures were followed, they were fully entitled to do."). "The federal courts ordinarily are empowered to review only an agency's *final* action, *see* 5 U.S.C. § 704, and the fact that a preliminary determination . . . is later overruled . . . does not render the decisionmaking process arbitrary and capricious." *Nat'l Ass'n of Home Builders*, 551 U.S. at 659. Agencies that change their mind are not "subjected to more searching review." *FCC v. Fox Television Stations, Inc.*, 556 U.S. 502, 514 (2009). What is important is that the agency "display awareness that it *is* changing position" and has explained itself. *Id.* at 515. EPA did not act arbitrarily and capriciously merely because it reversed course from its *2015 Proposed Rule*—a reversal that EPA explained.

Nor was the *2016 RHHRA* a final agency action. Human Health Risk Assessments are part of FIFRA reregistration review but are not in themselves safety determinations. *2016 RHHRA* at 3. It is the final Reregistration Eligibility Decision—which in this case was issued in 2006—that

serves as the final EPA action for determining safety pursuant to the FFDCA. *2006 Reregistration Decision* at 1–2. Although the *2016 RHHRA* stated that the studies cited by the petition provided "sufficient evidence that there are neurodevelopmental effects occurring at chlorpyrifos exposure levels below" current tolerances, this conclusion is tentative until the agency adopts it as part of a final order or rule. *2016 RHHRA* at 13. The *2016 RHHRA* remains part of a broader review process that will culminate in another Registration Eligibility Decision no later than 2022. In the meantime, however, relying on its Scientific Advisory Panel, EPA has explained why that study is flawed. The methodology used in the *2015 Proposed Rule* was rejected by the SAP, and the *2016 RHHRA* attempted to address the SAP's concerns by using a different approach. *Id.* at 3–4.

As it is entitled to do, EPA has sufficiently explained its rationale for reversing course from the *2015 Proposed Rule* and *2016 RHHRA* and denying the petition. EPA was required to "examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made." *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Ins. Co.*, 463 U.S. 29, 43 (1983) (quotations marks and citation omitted). EPA did articulate an explanation for its departure from the *2015 Proposed Rule* and the *2016 RHHRA* in its *2017 Denial* and *Final Order*. In its *2017 Denial* of the petition, EPA explained that responses from the 2016 SAP and comments received in response to the *2015 Proposed Rule* raised "considerable areas of uncertainty" regarding the studies. *2017 Denial*, 82 Fed. Reg. at 16,590. Based on this uncertainty, EPA concluded that it should instead "explore approaches raised by the SAP and commenters on the proposed rule, and possibly seek additional authoritative peer review of EPA's risk

assessment prior to finalizing any regulatory action in the course of registration review." *Id.*

EPA again explained the rationale for its departure from the *2016 RHHRA* in its *Final Order*. EPA explicitly recognized its denial of the petition was "at odds with" the *2016 RHHRA*, but it explained that it had "undertaken considerable efforts to assess the available chlorpyrifos data," summarizing its longstanding concerns about the studies relied on by petitioners. *Final Order*, 84 Fed. Reg. at 35,564. EPA discussed its decision to convene the SAP in 2016 to specifically consider the EPA's proposal to use information derived from the Columbia Study to develop a point of departure—a meeting EPA noted "was unique in focus compared to the previous meetings"—and the SAP's rejection of using that data alone as the basis for the new point of departure. *Id.* EPA explained that the 2016 SAP's feedback on the proposal based on the Columbia Study data was "consistent with concerns raised in public comments EPA received on the use of the epidemiology data throughout the course of registration review." *Id.* EPA further noted that, although the 2008 and 2012 SAPs recognized strengths in the Columbia Study, neither recommended changing points of departure based on the study, and the 2016 SAP expressed even more reservation about using the study in this way. *Id.* Thus, despite preliminary assessments that recognized potential in the Columbia Study data, EPA ultimately concluded that "the shortcomings of the data identified raise issues of validity, completeness and reliability under the FFDCA that direct against using the data for risk assessment at this time." *Id.* EPA also noted that this was not its final conclusion regarding the validity of the studies and that it "intends to continue its exploration of the uncertainty" with regards to the studies' conclusions. *Id.* Because these studies—which

met the threshold requirements for consideration on the merits—were not sufficiently valid, complete, and reliable to support revocation, EPA decided not to modify or revoke the chlorpyrifos tolerances.

Nothing in EPA's explanations is arbitrary or capricious. It is clear that the agency has struggled with the scientific studies before it. But nothing in either the procedure or the substance of EPA's actions—aside from playing Hamlet—suggests that the agency has been irresponsible. To the contrary, at every step of the way, EPA has conscientiously examined the evidence. In 2015, it told petitioners it would deny the petition outright. This was not surprising because EPA had long advised the petitioners and other interested persons of the flaws in the studies. It changed course later that year when it was forced to make a decision in response to our writ of mandamus. EPA then proposed revoking the chlorpyrifos tolerances based on a novel measure of the effect on infants and children—only to have the SAP disapprove of the measure in 2016 and recommend further study. EPA requested further comments on the science—and an extension of time to make a decision. When we told EPA that there would be no further extensions, EPA called for additional comments and repeated that the studies were inconclusive, but EPA continued to believe it had no choice but to revoke the tolerances. But even as it called for last comments, EPA advised that it was "still in the process of deliberating the provisions of a final rule." *2016 Request for Comments*, 81 Fed. Reg. at 81,051.

So how do we assess this convoluted history? It is certainly true that the agency had some stops and starts along the way, but that is evidence of deliberate decisionmaking, not dereliction of duty. We, of all institutions, should respect that there will be give-and-take in complicated matters of

consequence. The FFDCA does not demand unanimity within EPA, any more than it requires unanimity from this court before we may issue a judgment in this case.

In my view, the majority has intervened in ongoing debates within EPA over what the evidence proves and how it should be weighed. It is not our place to second-guess EPA's scientific assessment of laboratory and epidemiological studies supporting the petition. "Deference to an agency's technical expertise and experience is particularly warranted with respect to questions involving . . . scientific matters." *United States v. Alpine Land & Reservoir Co.*, 887 F.2d 207, 213 (9th Cir. 1989). When an agency makes determinations "within its area of special expertise, at the frontiers of science . . . a reviewing court must generally be at its most deferential." *Balt. Gas & Elec. Co. v. NRDC*, 462 U.S. 87, 103 (1983). The majority improperly makes its own assessment of the reliability of the studies and whether EPA's concerns are sufficient to determine that chlorpyrifos tolerances are "not safe." Maj. Op. 54–58, 60–63. But EPA's assessment of the scientific strength of the studies supporting the petition is precisely the type of analysis that should be given deference. FFDCA safety determinations are within EPA's area of expertise. We should not second-guess EPA's scientific conclusions with regards to the value of these studies. EPA's denial of the 2007 petition was neither arbitrary nor capricious.

* * *

The FFDCA does not require EPA to engage in a full-blown FFDCA safety evaluation in response to every petition filed with the agency. Instead, where a petition presents reasonable grounds for revocation, EPA must consider whether the petition puts forth data that supports a determination that a pesticide tolerance is not safe. Where

the data supporting a petition are not sufficiently valid, reliable, or complete, EPA may deny the petition and rest on its operative safety determination. Here, EPA complied with its statutory obligation: the agency considered the petition on the merits and determined that the data supporting the petition was insufficient to support revocation. Based on this determination, EPA denied the petition and relied on its 2006 finding that chlorpyrifos tolerances are safe. EPA explained the deficiencies in the underlying petition's supporting studies and its rationale for departing from its prior preliminary determinations. EPA did all that the FFDCA required.

III

Even if I thought the majority had read the statute correctly and had a clear-eyed view of the validity and weight to be given to the scientific evidence, the remedy ordered by the majority is an abuse of our discretion. Assuming that petitioners have demonstrated that chlorpyrifos is "not safe," the FFDCA gives EPA the discretion to decide whether to modify or to revoke the tolerance. *See* 21 U.S.C. § 346a(b)(2)(A)(i); Maj. Op. at 60 ("[O]nce the EPA has determined that a tolerance is not safe, . . . it must modify or revoke the tolerance."). Concluding that on this record "the present tolerances are not safe," Maj. Op. at 63, the majority orders EPA to "modify or revoke chlorpyrifos tolerances and modify or cancel chlorpyrifos registrations,"[9] Maj. Op. at 63, and gives EPA 60 days to do

[9] In ordering the modification or cancellation of FIFRA registrations, Maj. Op. at 67, the majority has exceeded the scope of what a petition under the FFDCA allows: modification or cancellation of chlorpyrifos *tolerances* under the FFDCA. *See* 21 U.S.C. § 346a(d)(1)(A) (allowing petitions "proposing the issuance of a

so, Maj. Op. at 67. It is more than a little ironic that this court will have taken over a year since the filing of the last brief to decide this case, but we will expect EPA to make an informed decision in the next 60 days.

The 60 days the majority gives EPA is not a number drawn from the statutes, but one made up by the majority, and it may well foreordain the option EPA must choose. In my view, the stakes in this case are too high for the majority to take upon itself to decide what the United States will do with respect to chlorpyrifos. "By pounds of active ingredient, [chlorpyrifos] is the most widely used conventional insecticide in the country" and for some crops it is "currently the only cost-effective choice for control of certain insect pests." *Final Order*, 84 Fed. Reg. at 35,558.[10] That, of course, is not an argument for finding chlorpyrifos safe, as EPA recognized, but it should sharpen our focus on what we are doing. *See 2017 Denial*, 82 Fed. Reg. at 16,590 ("Although not a legal consideration, it is important to recognize that for many decades chlorpyrifos has been and remains one of the most widely used pesticides in the United States, making any decision to retain or remove this pesticide from the market an extremely significant policy choice."). That is why EPA should be considering the options Congress

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regulation establishing, modifying or revoking a *tolerance*" under that statute (emphasis added)). Although modification of revocation of a tolerance under the FFDCA will necessarily impact registrations under FIFRA, the FFDCA does not afford this court authority to order modification or cancellation under FIFRA.

[10] Chlorpyrifos tolerances are classified by crop (*e.g.*, alfalfa, almonds, apples, corn, cotton, grapes, oranges, pears, soybeans, walnuts, and wheat) and usage (*e.g.*, cockroach and fire ant control, mosquito abatement, utility pole treatments) and are region specific. The complexity of the tolerances is difficult to overstate.

made available, not us. And we have not given anything but the most fleeting consideration to the options.[11]

It is far from clear that EPA will be able to do anything in the next 60 days other than revoke the tolerances. Yet, between argument and the issuing of this decision, EPA advised us that it has issued an interim decision to reregister chlorpyrifos, with modifications. *Pesticide Registration Review; Proposed Interim Decision for Chlorpyrifos; Notice of Availability*, 85 Fed. Reg. 78,849 (Dec. 7, 2020) (*2020 Proposed Interim Decision*) (inviting comments on EPA, *Chlorpyrifos: Proposed Interim Registration Review Decision* (Dec. 3, 2020) (*2020 Proposed Interim Registration*)). In the *2020 Proposed Interim Registration*, EPA explained that it was proceeding with suggested modifications, but that it still faced "numerous novel scientific issues, notably the potential for neurodevelopment effects on the young." *2020 Proposed Interim Registration Decision* at 10. Candidly, EPA stated:

> Despite several years of study, the science addressing neurodevelopmental effects remains unresolved. . . . Notwithstanding,

[11] The majority may have effectively foreclosed other options Congress made available to EPA. Under the FFDCA, if a petitioner can show that it not safe, EPA must modify or revoke the tolerance; or, in its periodic statutory review, if EPA cannot determine chlorpyrifos is safe, it cannot leave the tolerance in place. But if EPA arrives at that point, there is yet an additional option: EPA has the power to leave in effect or modify a tolerance if it concludes that certain consequences will follow—if "the residue protects consumers from adverse effects on health that would pose a greater risk than the dietary risk" or if the tolerance "is necessary to avoid a significant disruption in domestic production of an adequate, wholesome, and economical food supply." 21 U.S.C. § 346a(b)(2)(B)(iii). These contingencies would still require EPA to certify that the tolerances modified or left in effect satisfy the "no harm" to infants and children criteria in 21 U.S.C. § 346a(b)(2)(C).

> EPA recognizes that the science is evolving on this topic, and that there may be new information available prior to the completion of registration review that may impact the agency's conclusions about these effects.

Id. It further advised that it had convened a SAP in September 2020 "to assess new approval methodologies that might used to evaluate developmental neurotoxicity in EPA's assessment of risks to human health." *Id.*; *see also id.* at 40, 63. The SAP's report was issued a week later in December 2020. EPA, *FIFRA Scientific Advisory Panel Meeting Minutes and Final Report No. 2020-02*: *Peer Review of the Use of New Approach Methodologies (NAMs) to Derive Extrapolation Factors and Evaluate Developmental Neurotoxicity for Human Health Risk Assessment* (Sept. 15–18, 2020) (report released Dec. 15, 2020). For the reasons I have explained, in this latest proceeding, the risk of nonpersuasion runs against the existing tolerances. That means that EPA will have to decide the issues reserved in its interim proceedings—and, specifically, the question of safe tolerances for children and youth—and it must do so by 2022, the deadline set by Congress.

What effect the majority's order will have on EPA's latest proceeding is unclear, but the majority's order presents it with two unsatisfactory choices: either issue modified tolerances outside the procedure required by the FFDCA, FIFRA, and APA, or revoke the tolerances. Given the *2020 Proposed Interim Registration Decision*, maybe EPA will be comfortable issuing modified tolerances, but in order to do so it will have to accelerate its schedule, and that may mean skipping some steps. *See 2020 Proposed Interim Registration Decision* at 4, 8–9 (explaining that EPA is

awaiting revised biological opinions from the National Marine Fisheries Service and the U.S. Fish & Wildlife Service). Alternatively, EPA may be forced to revoke tolerances that it has tentatively concluded it will reregister or reregister with modifications. Perhaps EPA will again approve registration of chlorpyrifos at some future date once it completes full FIFRA and FFDCA review, but our precipitous order will have imposed tremendous costs on various sectors of the economy without waiting for the system to work.

Finally, I have to comment on the artificial schedule that our court has imposed on EPA, not only in this case, but time and again in these proceedings. EPA took the 2007 petition to revoke chlorpyrifos very seriously. Unlike reregistration under FIFRA, there is no statutory deadline for dealing with a petition, although in principle twelve years seems like more than enough time. The extraordinary delay, however, makes more sense in context: EPA initially believed that it could accelerate the FIFRA reregistration due in 2022 and address both the petition and the reregistration at the same time and well before that date. In the meantime, the petitioners asked us to intervene and order EPA to rule on its petition. EPA repeatedly advised us that it could not meet those demands if it was to complete the reregistration process properly. We insisted. Eventually, but reluctantly, EPA proposed to revoke the tolerances—even as it stated that it was doing so without complete information. *See, e.g.*, *2016 Request for Comments*, 81 Fed. Reg. at 81,050; *2015 Proposed Rule*, 80 Fed. Reg. at 69,080. After further proceedings, EPA concluded that it was better to deny the petitions outright because the petitioners had failed to show that the tolerances were not safe, and then complete the FIFRA reregistration process, where it would have a full record. EPA's decision is consistent with the FFDCA, as

amended by the FQPA. Although in hindsight the process took much longer than EPA anticipated, that was a reasonable decision on EPA's part at the time.

When we intervene in scientific inquiries with impatience and impose artificial deadlines, we bear some responsibility for the confusion that results. In *San Luis & Delta-Mendota Water Authority v. Jewell*, 747 F.3d 581 (9th Cir. 2014), the district court ordered the U.S. Fish & Wildlife Service to produce a complex, 400-page biological opinion in less than a year. The resulting biological opinion was

> a jumble of disjointed facts and analyses. It appears to be the result of exactly what we would imagine happens when an agency is ordered to produce an important opinion on an extremely complicated and technical subject matter covering multiple federal and state agencies and affecting millions of acres of land and tens of millions of people.

Id. at 605; *see also id.* at 605 n.15 (noting that "the FWS had less time to produce its opinion than either the district court or we will have had to review it"). We "wonder[ed] whether anyone was ultimately well-served by the imposition of tight deadlines in a matter of such consequence." *Id.* at 606. When we interject ourselves into technical proceedings, our "[d]eadlines become a substantive constraint on what an agency can reasonably do. . . . Such scientific tasks may not be as well suited to deadlines as producing written copy; the final product will necessarily reflect the time allotted to the agency." *Id.* We can only hope that "[f]uture analyses [will] be given the time and attention that these serious issues deserve." *Id.*

In any event, our order is an abuse of any discretion the APA confers on us. We have the power to "compel agency action . . . unreasonably delayed," 5 U.S.C. § 706(1), but we do not have the power to choose among the options available to EPA. Our deadline may effectively make the choice for EPA.

IV

There are manifest errors in the majority opinion. It has misread the FFDCA and misallocated the risk of nonpersuasion. It has overruled EPA's judgment on the validity and weight to be given technical evidence within EPA's expertise. And by its decision to give EPA 60 days to issue a final decision in this case, the majority has likely predetermined EPA's option. I respectfully, but firmly, dissent.

Agreement Reached to End Sale of Chlorpyrifos in California by February 2020

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FOR IMMEDIATE RELEASE

Use in agriculture to be prohibited after next year

Alternatives to Chlorpyrifos Work Group to hold public meeting in January

En Español

(Sacramento) – The California Environmental Protection Agency announced today that virtually all use of the pesticide chlorpyrifos in California will end next year following an agreement between the Department of Pesticide Regulation (DPR) and pesticide manufacturers to withdraw their products.

“For years, environmental justice advocates have fought to get the harmful pesticide chlorpyrifos out of our communities,” said Governor Gavin Newsom. “Thanks to their tenacity and the work of countless others, this will now occur faster than originally envisioned. This is a big win for children, workers and public health in California.”

“The swift end to the sale of chlorpyrifos protects vulnerable communities by taking a harmful pesticide off the market,” said California Secretary for Environmental Protection Jared Blumenfeld. “This agreement avoids a protracted legal process while providing a clear timeline for California farmers as we look toward developing alternative pest management practices.”

Earlier this year, DPR announced it was acting to ban use of chlorpyrifos by canceling the pesticide's product registrations. The decision follows mounting evidence, PDF that chlorpyrifos is associated with serious health effects in children and other sensitive populations at lower levels of exposure than previously understood, including impaired brain and neurological development.

At the same time, DPR and the California Department of Food and Agriculture (CDFA) have established a cross-sector working group to identify, evaluate and recommend safer, more sustainable pest management alternatives to chlorpyrifos. It will hold its first meeting this month and will hold three public workshops beginning in January.

The agreement with Dow AgroSciences and other companies means that use of chlorpyrifos will end sooner than anticipated had the companies pursued administrative hearings and potential appeals process, which could have taken up to two years. Under the settlement, the companies agreed that:

- All sales of chlorpyrifos products to growers in California will end on Feb. 6, 2020.
- Growers will no longer be allowed to possess or use chlorpyrifos products in California after Dec. 31, 2020.
- Until then, all uses must comply with existing restrictions, including a ban on aerial spraying, quarter-mile buffer zones and limiting use to crop-pest combinations that lack alternatives. DPR will support aggressive enforcement of these restrictions.

To ensure consistency for growers and for enforcement purposes, DPR is applying the terms and deadlines in the settlements to seven other companies that are not part of the settlement agreement but are subject to DPR's cancellation orders.

A few products that apply chlorpyrifos in granular form, representing less than one percent of agricultural use of chlorpyrifos, will be allowed to remain on the market. These products are not associated with detrimental health effects. DPR will continue to monitor for any exposures associated with these products.

The development of safe, more sustainable alternatives to chlorpyrifos is being supported through the current state budget, which appropriates more than $5 million in grant funding for the purpose.

- DPR will award more than $2.1 million in grants to fund projects that identify, develop, and implement safer, practical, and sustainable pest management alternatives to chlorpyrifos.
- CDFA will award approximately $2 million in grants to expand outreach about innovative, biologically integrated farming systems that reduce chemical insecticide inputs. Crops that have used chlorpyrifos will be a priority.
- CDFA will also fund approximately $1.5 million in research to develop alternatives to chlorpyrifos that provide safer, more sustainable pest management solutions.

Quick facts:

- Chlorpyrifos is used to control pests on a variety of crops, including alfalfa, almonds, citrus,

cotton, grapes and walnuts. It has declined in use over the past decade as California growers have shifted to safer alternatives.

- Use of the pesticide dropped more than 50 percent from two million pounds in 2005 to just over 900,000 pounds in 2017.
- In 2015, DPR designated chlorpyrifos as a "restricted material" that requires a permit from the county agricultural commissioner for its application. In addition, application of chlorpyrifos must be recommended by a licensed pest control advisor and supervised by a licensed certified applicator.
- Following DPR's designation of chlorpyrifos as a toxic air contaminant in 2018, DPR recommended that county agricultural commissioners apply additional permit restrictions, including a ban on aerial spraying, quarter-mile buffer zones and limiting use to crop-pest combinations that lack alternatives.

###

EU to Ban Chlorpyrifos Pesticide Starting in February

bloomberglaw.com/bloomberglawnews/environment-and-energy/XFIQR4N0000000

Dec. 6, 2019, 6:43 AM

- EU prohibition on chlorpyrifos confirmed by committee vote
- Trade in pesticides no longer permitted in EU after Jan. 31

The European Union confirmed it will no longer permit sales of the widely-used insecticide chlorpyrifos after Jan. 31, 2020.

In a regulatory committee vote Dec. 6, EU countries backed the withdrawal of the authorization for the chlorpyrifos and and the related substance chlorpyrifos-methyl, which have been identified as a possible cause of neurological damage in children.

The move was expected after the European Food Safety Authority (EFSA), which carries out pesticide risk assessments, said in August that no safe exposure level existed for chlorpyrifos, which is used widely on fruit, corn, and other crops.

The prohibition will hit Corteva Agriscience, Adama Agriculture BV, and Sapec Agro SA, which applied for reapproval of chlorpyrifos.

“This decision denies EU growers access to yet another key tool to protect their crops,” said Corteva spokesman József Máté in an email to Bloomberg Environment. Corteva sells chlorpyrifos under the Lorsban brand name.

The European Commission, the EU’s executive arm which will formally finalize the prohibition, welcomed the committee decision, spokeswoman Vivian Loonela said. Details about how many EU countries backed the prohibition weren’t immediately known, she said.

Out of Step With EPA

The European food agency's findings on the pesticide were out of step with the U.S. Environmental Protection Agency and the Australian Pesticides and Veterinary Medicines Authority, Corteva's Máté said.

The EPA said in July that data supporting objections to the use of the pesticide was "not sufficiently valid, complete or reliable."

But DowDupont Inc. and other chemical manufacturers next year will stop selling chlorpyrifos in California. The action follows the state's move to set new allowable levels in order to reduce exposures to bystanders, workers, and the environment.

But environmental groups say evidence justifying a ban on chlorpyrifos is overwhelming because of its impacts on children's development.

"The EU is the largest single market in the world and the most powerful trading power, so we hope this ban will pave the way to other bans elsewhere in the world," said Nabil Berbour, campaign manager of corporate responsibility watchdog SumOfUs.

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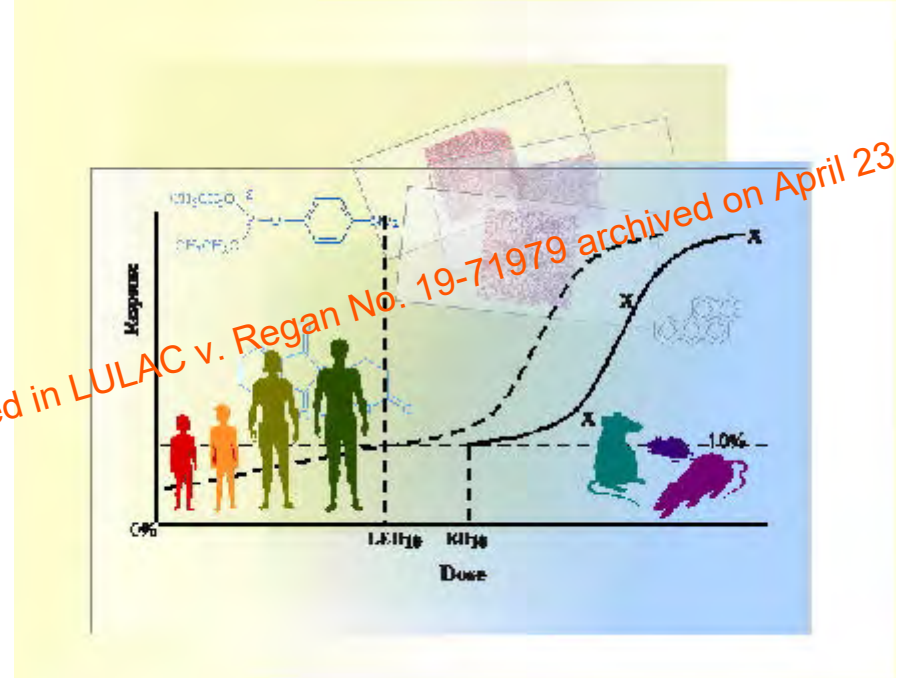
HUMAN HEALTH RISK ASSESSMENT

CHLORPYRIFOS



U.S. Environmental Protection Agency
Office of Pesticide Programs
Health Effects Division (7509C)

Deborah C. Smegal, M.P.H., Risk Assessor
June 8, 2000

HUMAN HEALTH RISK ASSESSMENT

CHLORPYRIFOS

Phase 4

Risk Assessment Team:

Lead Risk Assessor:	Deborah C. Smegal, M.P.H., Toxicologist
Dietary Risk:	David Soderberg, Chemist
Residue Chemistry:	Steven Knizner, Senior Scientist/Chemist
Product Chemistry:	Steven Knizner, Senior Scientist/Chemist
Agricultural, Occupational and Residential Exposure:	Timothy Leighton, Environmental Health Scientist
	Deborah C. Smegal, M.P.H., Toxicologist
Toxicology:	Deborah C. Smegal, M.P.H., Toxicologist
Incident Review:	Jerome Blondell, Health Statistician
	Virginia Dobozy, Veterinary Medical Officer

Management:

Senior Scientist:	Steven Knizner
Branch Chief:	Jess Rowland
Division Director:	_____
	Margaret J. Stasikowski, June 8, 2000

Background

Attached is HED's risk assessment of the organophosphate pesticide, chlorpyrifos, for purposes of issuing a Reregistration Eligibility Decision (RED) Document for this active ingredient. Cumulative risk assessment considering risks from other pesticides or chemical compounds having a common mechanism of toxicity is not addressed in this document. This risk assessment updates the October 18, 1999 version and addresses the Public Comments in accordance with Phase 3 of the Tolerance Reassessment Advisory Committee (TRAC) Organophosphate (OP) Pilot Process. EPA and the registrants have agreed to certain modifications to the use of chlorpyrifos to mitigate dietary, worker and residential risks. This risk assessment incorporates elements of the risk mitigation agreement in a number of its analyses in order to characterize post-mitigation risks. The disciplinary science chapters and other supporting documents for the chlorpyrifos RED are also included as attachments as follows:

- Report of the Hazard Identification Assessment Review Committee. D. Smegal (4/6/2000, HED Doc No. 014088)
- Report of the FQPA Safety Factor Committee. Brenda Tarplee (4/4/00; HED Doc No. 014077)
- Revised Product and Residue Chemistry Chapter. Steven Knizner (June 2000)
- Toxicology Chapter. Deborah Smegal (4/18/00; D263892)
- Occupational/Residential Handler and Post-Application Residential/Non-Occupational Risk Assessment. D. Smegal/T. Leighton (June 2000; D266562)
- Agricultural and Occupational Exposure Assessment: Tim Leighton (June 2000; D263893)
- Acute Dietary Risk Assessment for Chlorpyrifos. (D. Soderberg June 2000, D263890)
- Chronic Dietary Exposure Assessment for Chlorpyrifos. D. Soderberg (June 2000, D263889)
- Chlorpyrifos Incident Review Update: Jerome Blondell (4/20/00).
  Update of Incident Data on Chlorpyrifos for Domestic Animals. Virginia Dobozy (04/26/99; D255514)
- Analysis of Chlorpyrifos IDS Data for Domestic Animals. Virginia Dobozy (1/23/95)
- Drinking Water Assessment from the Environmental Fate and Effects Division (EFED). Michael Barrett (11/13/98)

‘ EFED Concerns over well contamination associated with termiticide use and EFED Recommended Concentrations for HED Drinking Water Assessment of Chlorpyrifos. Henry Nelson (10/6/99)

‘ Chlorpyrifos Preliminary Risk Assessment for Trichlorpyridinol (TCP) Metabolite. S. Knizner. D265035.

HED’s Hazard Identification Assessment Review Committee (HIARC) reviewed the toxicological database for chlorpyrifos and selected toxicological endpoints for acute oral, chronic oral and for short-, intermediate and long-term dermal and inhalation exposure risk assessment in February 1999, and January 2000 (memorandum dated April 6, 2000). HED’s FQPA Safety Factor Committee reviewed the hazard and exposure data for chlorpyrifos on January 24, 2000, and deferred to the Office of Pesticide Programs Division Directors and senior scientists (DD-SS). The DD-SS recommended that the 10X FQPA Safety Factor (as required by Food Quality Act of August 3, 1996) be retained in assessing the risk posed by this chemical (memorandum dated April 4, 2000).

In June 1997, the registrants of chlorpyrifos voluntarily agreed to measures designed to reduce household exposure to chlorpyrifos, as part of a risk reduction plan. This voluntary plan included deletion of indoor broadcast use, use as an additive to paint, direct application to pets (sprays, shampoos and dips), and indoor total-release foggers. The technical chlorpyrifos products have been amended to reflect the negotiated plan. The technical label limits end use product labeling to only those sites which are specified on its label. In addition, the registrants have implemented measures to improve education, training, and labels, and report and analyze incidents. In addition, as part of this agreement, the registrants agreed to work with EPA to develop broad, market-wide policies for all indoor insecticides for a number of areas.

EPA and the registrants have agreed to certain modifications to the use of chlorpyrifos to mitigate dietary, worker and residential risks. This risk assessment incorporates elements of this agreement in a number of its analyses in order to characterize post-mitigation risks. The agreement includes:

‘ Agricultural Uses

- Restrict use on apples to pre-bloom (dormant) application only
- Cancel use on tomatoes
- Implement revised restricted-entry intervals for all agricultural crops.

‘ Non-Agricultural Uses

- Cancel all indoor residential uses (except fully contained ant baits in child resistance packaging).
- Cancel all outdoor residential uses (except limited public health uses).
- Cancel all indoor and outdoor non-residential uses (e.g. FHE) except:
- Use on golf courses
- Limited public health uses
- Limited use in industrial settings (e.g. manufacturing plants, ship holds)
- Cancel whole house “post-construction” termiticide use.
- Phase out limited post-construction spot and local termiticide treatments
- Phase out pre-construction termiticide treatments
- Reduce the maximum application rate for phased-out termiticide treatments to a 0.5% concentration.
- Reduce the maximum application rate for use on golf courses to 1 lb. active ingredient per acre.

In addition to these agreed upon actions the Agency will also propose to revoke the tolerance on tomatoes and reduce the tolerances on apples and grapes to 0.01 ppm. These changes were also included in the analysis of post-mitigation dietary exposure.

CHLORPYRIFOS REVISED RISK ASSESSMENT

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CHLORPYRIFOS

1.0 Executive Summary

Background

The Health Effects Division (HED) has conducted a Human Health Risk Assessment for the active ingredient chlorpyrifos for the purposes of making a reregistration eligibility decision (RED). The toxicological database is complete and adequate to support reregistration in accordance with the Subdivision F Guidelines for a food use chemical. Residue chemistry requirements are substantially complete pending receipt of limited confirmatory data.

Chlorpyrifos, [O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl)-phosphorothioate], is a broad-spectrum, chlorinated organophosphate insecticide that was first registered in 1965 to control foliage- and soil-borne insect pests on a variety of food and feed crops. Chlorpyrifos' most common trade names are Dursban, Empire 20, Equity, and Whitmire PT 270. Lorsban is a trade name for agricultural-use products. It is one of the most widely used organophosphate insecticides in the U.S., and is one of the major insecticides used in residential settings. Approximately 21 to 24 million pounds are used annually in the U.S, of which approximately 11 million pounds are applied in non-agricultural settings. There are approximately 800 registered products containing chlorpyrifos on the market. Registered uses include: variety of food crops (i.e., there are approximately 112 tolerances for food/feed commodities); turf and ornamental plants; greenhouses; sodfarms; indoor pest control products (e.g., crack and crevice); structural pest control (e.g., termites); and pet collars. It is registered for use in residential and commercial buildings, schools, daycare centers, hotels, restaurants and other food-handling establishments, hospitals, stores, warehouses, food manufacturing plants, vehicles, and livestock premises. In addition, it is used as a mosquitocide, and as impregnated in ear tags for cattle. In 1998, Dow AgroSciences (DAS) estimated that 70% of the urban chlorpyrifos use involved termite control. Chlorpyrifos products are widely used by homeowners and professionals.

The following are formulation types for chlorpyrifos: wettable powder, emulsifiable concentrate, dust, granular, bait, flowable concentrate, impregnated material, pelleted/tableted, pressurized liquid, and microencapsulated. Dry flowable and wettable powder formulations in open bags are no longer supported by the primary registrant, Dow AgroSciences (DAS). Therefore, these formulations are not assessed in this risk assessment and are not eligible for re-registration.

Hazard

Chlorpyrifos is moderately toxic following acute oral, dermal and inhalation exposures (toxicity category II). Chlorpyrifos affects the nervous system by reversibly inhibiting the activity of cholinesterase (ChE), an enzyme necessary for the proper functioning of the nervous system. Inhibition of ChE is the most sensitive effect in all animal species evaluated and in humans, regardless of route or duration of exposure. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition. Data from two human studies suggest that humans are similarly and possibly more sensitive than animals following acute and short-term oral exposure and acute dermal exposure based on plasma ChE inhibition and/or possible clinical signs. Females are slightly more sensitive than males based on ChE inhibition and acute toxicity (comparison of LD_{50}'s). Studies in the scientific literature suggest that neonates are more sensitive to oral chlorpyrifos exposure than adults for ChE inhibition and behavioral effects. The increased sensitivity of the young may be attributed to a reduced capacity to detoxify chlorpyrifos.

Developmental and reproductive effects have been observed in rats, rabbits and/or mice, but only at doses that induced maternal or parental toxicity. In rats, chlorpyrifos causes delayed alterations in brain development in offspring of exposed mothers. Several studies in the peer reviewed literature and results of the guideline developmental neurotoxicity study are supportive of the possibility that chlorpyrifos exposure may affect brain development (e.g., altered synaptic development, alterations in DNA, RNA, and protein synthesis, inhibition of mitosis and mitotic figures, and disruption of the structural architecture of the brain). There are suggestive data that these effects may arise independent of cholinesterase inhibition.

Chlorpyrifos did not induce treatment-related tumors or provide evidence of carcinogenicity in two chronic rat or two chronic mouse studies. Chlorpyrifos was not mutagenic in bacteria, or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria.

For the purposes of this assessment, HED has concluded that the primary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), is not of toxicologic concern because 3,5,6-TCP does not induce cholinesterase inhibition (58 FR 19354, April 14, 1993). However, because of potential exposure to TCP in food and residential settings, and evidence of increased susceptibility of rabbit fetuses relative to dams based on the DAS-submitted rabbit developmental study, HED conducted a screening-level risk assessment for TCP. This assessment is attached in memorandum from S. Knizner to D. Smegal, D265035 June 5, 2000.

The toxicity endpoints used in this document to assess hazards include acute dietary and chronic dietary reference doses (RfDs), and short-, intermediate- and long-term dermal and inhalation doses. In light of the developing Agency policy on use of toxicology studies employing human subjects, HED selected doses and endpoints for risk assessment based solely on animal studies. Therefore, this document contains risk

assessments based on animal toxicity studies.

The acute dietary RfD of 0.005 mg/kg/day is based on a no-observed adverse effect level (NOAEL) of 0.5 mg/kg/day from an acute oral rat blood time-course study that observed 28-40% plasma cholinesterase (ChE) inhibition 3-6 hours after dosing male rats with a single dose of 1 mg/kg/day (the lowest-observable adverse effect level, LOAEL). This NOAEL is supported by statistically significant 30% RBC ChE inhibition 4 hours after a single 1.5 mg/kg/day exposure by a study in the scientific literature (Zheng et al. 2000). The chronic RfD of 0.0003 mg/kg/day is based on an oral NOAEL of 0.03 mg/kg/day for significant plasma and red blood cell (RBC) ChE inhibition at 0.22 to 0.3 mg/kg/day (LOAEL) based on a weight of the evidence consideration of 5 toxicity studies in dogs and rats. An uncertainty factor of 100 (10X for interspecies extrapolation and 10X for intraspecies variability) was applied to the NOAELs to obtain the RfDs.

A route-specific short-term dermal NOAEL of 5 mg/kg/day from a 21-day dermal rat study has been selected based on plasma and RBC ChE inhibition of 45% and 16%, respectively at 10 mg/kg/day (LOAEL). A dermal absorption adjustment is not necessary because a dermal study was selected. The intermediate- and long-term dermal NOAELs and long-term inhalation NOAEL are 0.03 mg/kg/day based on statistically significant plasma and RBC ChE inhibition that occurred at 0.22 to 0.3 mg/kg/day based on a weight of the evidence of 5 toxicity studies in dogs and rats. Because an oral NOAEL was selected, a 3 percent dermal absorption factor was used. Dermal absorption was estimated to be 3 percent based on the ratio of the oral LOAEL of 0.3 mg/kg/day from the rat developmental neurotoxicity (DNT) study to the dermal LOAEL of 10 mg/kg/day from the 21-day rat dermal study. This absorption factor is comparable to the dermal absorption estimated from human data of 1-3%.

The short- and intermediate-term inhalation NOAEL is 0.1 mg/kg/day from two separate 90-day rat inhalation studies that did not observe effects at the highest vapor concentration tested. HED selected a LOAEL of 0.3 mg/kg/day for 43% plasma and 41% RBC ChE inhibition from the oral developmental neurotoxicity study in rats to complete the dose-response assessment. A 100% default inhalation absorption factor (i.e., inhalation and oral absorption are equivalent) was used.

FQPA Safety Factor

The Food Quality Protection Act (FQPA) Safety Factor Committee re-evaluated the previous FQPA safety factor recommendation based on new hazard information, and deferred to the OPP Division Directors and several Agency senior scientists (DD-SS group) for the recommendation. The Division Directors and senior scientists (DD-SS group), recommended that the FQPA safety factor should be **retained at 10X** for the protection of infants and children from exposure to chlorpyrifos. The FQPA safety factor is applicable to **females 13-50, and infants and children** population subgroups for acute and chronic dietary risk assessments and residential and other non-occupational risk assessments of all durations. The safety factor was retained because new data in the

literature (Zheng et al. 2000) demonstrated increased neonatal sensitivity following a low-level single oral exposure, and a registrant submitted developmental neurotoxicity (DNT) study showed a clear qualitative difference in response (i.e., susceptibility) between adult rats and their offspring. Cholinesterase inhibition was observed in dams versus structural effects in the developing brain of the offspring.
In addition, the new data in the literature also gave rise to uncertainties such as the suggestion that the inhibition of cholinesterase may not be essential for adverse effects on brain development; and the lack of an offspring NOAEL in the DNT based upon structural alterations in brain development as the toxicity endpoint of concern (i.e., effects were seen at the lowest dose evaluated).

Dietary Exposure and Risk

HED conducted the most highly refined acute probabilistic and chronic deterministic dietary (food) exposure analyses possible using the Dietary Exposure Evaluation Model (DEEM). Both the acute and chronic dietary analyses incorporate monitoring data obtained from U.S. Department of Agriculture's (USDA's) Pesticide Data Program (PDP), the Food and Drug Administration's (FDA's) Surveillance Monitoring Program, in addition to monitoring data from Dow AgroSciences' (DAS')1993 National Food Survey (NFS) (a market basket survey), and field trial data for a limited number of crops. Percent crop treated data and processing and cooking factors were also used to refine the exposure estimates. The Agency's acute and chronic analyses incorporated PDP and FDA monitoring data to the greatest extent possible, and NFS data for seven of the nine commodities included in the survey (milk, apple juice, applesauce, orange juice, ground beef, pork sausage and peanut butter). The NFS data for fresh apples were also included in a sensitivity analysis. The NFS tomato data were not included because only 54 samples were collected from Florida, while more extensive and recent data for fresh tomatoes are available from PDP (881 samples, collected in 1996 and 1997). PDP monitoring data also reflect the use of chlorpyrifos on imported fresh tomatoes (a significant source of fresh tomatoes). Therefore the PDP fresh tomato residue data were used exclusively in all analyses.

Three data sets are available for estimating residues on fresh apples: PDP data for analysis of individual single apples; PDP “decomposited” apple data; and NFS “decomposited” apple data. Use of each of these three data sets for fresh apples leads to a different exposure estimate. The dietary exposure analysis has been performed using all commodities having chlorpyrifos uses and each of the apple data sets separately: PDP data for single apples; PDP “decomposited” apple data; and NFS “decomposited” apple data.

In both acute and chronic risk assessments, exposure was compared to a population adjusted dose, (PAD), which is the reference dose (RfD) reflecting retention of the FQPA 10x factor for females and children. HED considers dietary residue contributions greater than 100% of the PAD to be of concern. The acute and chronic PADs are 0.0005 and 0.00003 mg/kg/day, respectively for children and females 13-50 years. The acute and chronic PADs are 0.005 and 0.0003 mg/kg/day, respectively for all

other population groups. The Agency's highly refined **acute dietary exposure** estimates at the 99.9th percentile were greater than 100% of the aPAD for all child subpopulations based on the 1999 PDP single apple data, the decomposited 1994-1997 PDP apple data, and/or the decomposited 1993-1994 NFS apple data. Children 1-6 years old were the most highly exposed population subgroup, regardless of which data set is used for fresh apples. Apples contribute most to the child risk estimates. For **children 1-6 years** old, risk estimates ranged from **170% to 355% of the aPAD** depending on which fresh apple data set was used. Use of PDP's 1999 single apple data resulted in the highest exposure estimates. Use of the decomposited NFS fresh apple data resulted in the lowest exposure estimates. Because the PDP single apple data are the most recent and do not require decompositing, these data are expected to provide the most reliable exposure and risk estimates. However, no matter which of the three data sets is used for fresh apples, the critical exposure commodity (CEC) analysis indicated that residues on fresh apples were the major contributor to dietary exposure estimates for children 1-6 years old at the 99.9th percentile exposure. Residues on whole tomatoes and grapes were the next major contributors to exposure.

Various risk mitigation measures were examined to reduce acute dietary exposure and risk estimates. Risk estimates could be reduced to less than 100% of the aPAD for children 1-6 years old only with mitigated exposures from consumption of fresh apples, grapes and tomatoes. Acute dietary risk estimates for children 1-6 years old were reduced to 82% of the aPAD based on the following mitigation measures: reduction of the apple tolerance to 0.01 ppm based on dormant application only; reduction of the grape tolerance to 0.01 ppm based on the domestic use pattern; and deletion of the use and removal of the tolerance on tomatoes. Ingestion of residues detected on a number of commodities (spinach, squash and carrots) that lack chlorpyrifos tolerances does not impact the acute dietary risk estimates. Because chlorpyrifos is not registered for use on these crops, these residues represent chlorpyrifos misuse or possibly spray drift.

The Agency's average **chronic dietary exposure** estimates for the U.S. population and all subgroups, with or without consideration of food handling establishment use, **are below HED's level of concern.** Without consideration of the food handling establishment (FHE) use, the average exposure estimates comprised 3% of the cPAD for the general population and 61% of the cPAD for the most highly exposed subgroup, children 1-6 years old. The Agency average exposure estimates including the food handling establishment use comprised 4% of the cPAD for the general population and **81% of the cPAD** for the most highly exposed subgroup, children 1-6 years old. The risk mitigation measures designed to reduce acute dietary risk also reduce chronic dietary risk. Children 1-6 years old remain the most highly exposed subpopulation, with risk estimates of 51% and 31% of the cPAD, including the FHE use or using zero residues for the FHE use, respectively. Ingestion of residues on a number of commodities (spinach, squash and carrots) that lack chlorpyrifos tolerances does not impact the chronic dietary risk estimates.

Drinking Water Exposure and Risk

The available environmental fate data suggest that chlorpyrifos has a low potential to leach to groundwater in measurable quantities from typical agricultural uses, however, there have been instances of well contamination following termiticide use. The available data indicate that the primary metabolite of chlorpyrifos, 3,5,6-TCP is more mobile, and significantly more persistent in many soils, especially under anaerobic conditions. The Agency has provided a screening-level drinking water assessment based on simulation models and an analysis of available monitoring data to estimate the potential concentrations of chlorpyrifos in ground and surface water.

The Agency conducted an analysis of over 3000 filtered groundwater monitoring well data available in U.S. Geological Survey's National Water Quality Assessment (NAWQA) Program databases, and in the Agency's Pesticides in Ground Water Data Base (PGWDB). Chlorpyrifos was infrequently detected in groundwater (< 1% of the 3000 wells), with the majority of concentrations reported to be <0.01 ppb, and a maximum detected concentration of 0.65 ppb in the PGWDB. Groundwater concentrations following termiticide use are potentially much higher, with a maximum reported concentration of 2090 ppb because of well contamination. The Agency also performed screening-level model estimates of chlorpyrifos concentrations in groundwater using SCI-GROW. Inputs to the models included high exposure agricultural scenarios for major crops (alfalfa, corn, citrus, and tobacco) at the maximum application rates. The estimated concentrations of chlorpyrifos in groundwater using the SCI-GROW screening model range from 0.007 to 0.103 ppb.

The Agency also evaluated more than 3000 samples from 20 NAWQA study units for surface water. In surface water, chlorpyrifos was detected at frequencies up to 15% of 1530 agricultural streams, 26% of 604 urban stream samples in 1997 and in 65% of 57 urban stream samples from Georgia, Alabama and Florida in 1994. The maximum reported dissolved chlorpyrifos concentration in surface water is 0.4 ppb, with the 95th percentile at 0.026 ppb, and the majority of concentrations < 0.1 ppb. However, the Agency notes that the monitoring data are not available for the most vulnerable watersheds or groundwater where chlorpyrifos use is pervasive. The Agency also performed screening-level model estimates of chlorpyrifos concentrations in surface water using Tier I GENEEC or Tier II PRZM/EXAMS. Estimated maximum 90 day average and peak concentrations of chlorpyrifos in surface water using the PRZM/EXAMS screening model are 6.7 Fg/L and 40.6 ppb, respectively.

Based on the monitoring data and model estimates the Agency used a range of upper-bound estimated environmental concentrations (EECs) in water for the water assessment. For the acute and chronic groundwater assessment an EEC range of 0.007 to 0.103 ppb was used based on screening-level model estimates. For the acute surface water assessment a range of 0.026 to 0.4 ppb was used, based on the 95th percentile and maximum reported concentrations from monitoring data. For the chronic surface water assessment, the 95th percentile concentration from monitoring data of 0.026 ppb was used. For termiticide use, the Agency had upper-bound groundwater concentrations of 30 to 2090 ppb for the acute exposures, based on well remediation efforts and monitoring data, respectively, and 8.3 to 578 ppb (acute values adjusted for partial environmental

degradation) for chronic exposures. The SCIGROW model and the monitoring data do not reflect actual drinking water concentrations after dilution (from source to tap) or drinking water treatment.

HED calculated drinking water levels of comparison (DWLOCs) assuming mitigation measures for diet and residential uses. Except for possible contamination resulting from termiticide use, the acute and chronic DWLOCs are greater than the EECs and thus do not exceed HED's level of concern.

Exposures to chlorpyrifos from groundwater because of well contamination as a result of the termiticide use for either acute or chronic durations may result in exposures that are potentially of concern. However, implementation of PR-96-7 has reduced the reported incidents of groundwater contamination resulting from termiticide treatment.

Occupational and Residential Exposure and Risk

Occupational and residential exposures to chlorpyrifos can occur during handling, mixing, loading and application activities. Occupational postapplication exposure can occur for agricultural workers re-entering treated fields such as during scouting, irrigation and harvesting activities.

Residential postapplication exposure can occur following treatment of lawns, or residences for cockroaches, carpenter ants, termites, and other insects. In addition, there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated turf and soil or licking fingers following contact with treated areas. Postapplication exposure to children can occur in locations other than the home, including schools, daycare centers, playgrounds, and parks.

There is insufficient use information and exposure data to assess exposure resulting from use in vehicles (i.e., planes, trains, automobiles, buses, boats) and other current label uses such as treatment of indoor exposed wood surfaces, supermarkets, theaters, furniture, and draperies, etc. HED has concern for these uses based on the residential scenarios assessed within this document, which show that nearly all current uses evaluated result in exposures that exceed HED's level of concern. HED has requested additional exposure data for all registered uses not evaluated in this assessment. Although there is concern for these uses, the Agency believes that exposure to these uses will not be higher than the scenarios evaluated in the risk assessment.

HED has conducted dermal and inhalation exposure assessments for: occupational and residential handlers; occupational postapplication; and residential postapplication dermal and inhalation exposure to adults and children as well as inadvertent oral exposure to children. The exposure duration for short-term assessments is defined as 1 to 30 days. Intermediate-term durations are 1 month to six months, and long-term exposures are durations greater than six months. The duration of exposure is expected to be: short-term for agricultural handlers; intermediate and long-term for the occupational handler in residential settings (i.e., lawn care operator and pest control operator); intermediate-term

for occupational postapplication; and short-term for the residential handler. The postapplication residential exposures evaluated in this assessment are considered short-term, except for exposures from termiticide treatment which is considered a long-term exposure.

For the dermal and inhalation risk assessment, risk estimates are expressed in terms of the Margin of Exposure (MOE), which is the ratio of the NOAEL selected for the risk assessment to the exposure level. For occupationally exposed workers, MOEs >100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. For residential populations, MOEs >1000, which includes the 10x FQPA safety factor for females 13-50 and children, do not exceed HED's level of concern. The target MOE of 1000 is applicable for residential handlers.

The **majority of occupational risk estimates do not exceed HED's level of concern** with appropriate personal protective equipment (PPE) or engineering controls. The results of the short-term handler assessments indicate that only 1 of the 16 potential exposure scenarios did not provide at least one application rate with a total MOE(s) greater than or equal to 100 at either the maximum PPE (i.e., coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems) or using engineering controls (i.e., closed systems). In the majority of cases, dermal exposure contributes more significantly to the total MOE than inhalation exposure.

In total, exposure and risk estimates were calculated for 56 scenarios. Based on the maximum level of protection (i.e., various levels of PPE or engineering controls) 2 MOEs are estimated to be less than 10; 6 MOEs are between 10 and 50; 9 MOEs are between 50 and 100, and 39 MOEs are greater than 100. Fourteen of the scenarios were evaluated based on data obtained from five chemical-specific studies submitted by DAS. The agricultural handler assessments are believed to be reasonable high end exposure representations of chlorpyrifos uses.

There is insufficient information (e.g., dermal and inhalation exposure data) to assess 3 scenarios: seed treatment uses, dip applications (e.g., preplant peach root stock, and nursery stock), and dry bulk fertilizer applications to citrus orchard floors. Given the results from the other scenarios assessed, these scenarios may also need to be mitigated. HED has requested data for these scenarios.

The results of the **Pest Control Operator (PCO)/Lawn Care Operator (LCO) handler assessment in residential/recreational settings** for short-, intermediate and/or long-term exposure scenarios indicate that **most** of the MOEs are less than 100, and therefore **exceed HED's level of concern**. The only scenarios that result in MOEs above 100, and do no exceed HED's level of concern are: (1) lawn care professionals that wear PPE and mix and load liquid lawn products (but do not apply) (total MOEs 100-820), (2) workers who mix/load or apply chlorpyrifos for aerial mosquitocide applications of less than 30 days with the use of engineering controls (closed systems)(total MOEs 160-240); (3) workers who mix/load or apply chlorpyrifos for ground-based fogger mosquitocide

applications up to several months with the use of PPE or engineering controls (total MOEs 100-560), and (4) most golf course workers who use the typical rate of 1 lb ai/acre or mixer/loaders of wettable powder that handle product to treat 4 lb ai/acre for less than 30 days (total MOE 100-400).

A number of risks were estimated based on chemical-specific biomonitoring studies submitted by DAS (i.e., indoor crack and crevice treatment, broadcast turf application, and pre- and post-construction termiticide treatment) in which the LCOs/PCOs wore label-specified PPE or PPE in addition to that specified on labels. Several of these studies did not apply the product at the maximum label rate, or only evaluated exposures for a few hours (i.e. 1-3 hours) of the work day, and consequently could underestimate exposures and risks to LCOs/PCOs. Overall, the exposures and risk estimates for LCOs/PCOs based on the chemical-specific biomonitoring studies are considered to be central tendency estimates because they evaluated less than a full day's exposure at the maximum label rate. In the absence of chemical-specific data, LCO/PCO exposures were estimated using data from Pesticide Handlers Exposure Database (PHED) or the Draft Residential SOPs.

The results of the **short- and intermediate-term postapplication** assessments for **workers at agricultural use sites** indicate that restricted entry intervals (REIs) need to be established. REIs represent the duration in days which must elapse before the Agency would not have a concern (MOE $100) for a worker wearing a long-sleeved shirt and long pants to enter the treated area and perform specific tasks. The **REIs range from 24 hours** for the low, medium, and high crop grouping matrix **to 10 days** for harvesting cauliflower. In short, REIs are 24 hours for all crops except the following: cauliflower (10 days), all nut trees (2 days), all fruit trees (4 days), and citrus (5 days). The occupational postapplication assessment is believed to be reasonable high end representations of chlorpyrifos uses. Four registrant-submitted dislodgeable foliar residue (DFR) studies are included in this assessment. Specifically, data are available for sugar beets, cotton, sweet corn, almonds, pecans, apples, citrus, cauliflower, and tomatoes. The short-term MOEs for postapplication exposure for mow/maintenance workers at golf courses are above 100 (110-210) and therefore, do not exceed HED's level of concern, even at the maximum label rate of 4 lb ai/acre.

All nine short-term residential handler exposure scenarios evaluated have total dermal and inhalation MOEs (based on typical, and maximum usage rates) that **exceed HED's level of concern** defined by a target MOE of 1000. MOEs for the residential handler ranged from 3 to 900 for dermal risk, from 120 to 57,000 for inhalation risk, and from 3 to 880 for total dermal and inhalation risk. The following scenarios were evaluated: (1) indoor crack and crevice treatment, (2) lawn treatment with liquid products, (3,4,5) lawn treatment with granular formulations via push-type spreader, belly grinder and hand application, (6) application of ready to use products, (7) dust product applications, (8) paintbrush application, and (9) treatment of ornamentals. In some instances, when the product is not applied at the maximum label rate, the MOEs are above 1000 (i.e., 2 oz crack and crevice spot treatment with a MOE of 1600). Only one of the residential handler

scenarios was evaluated using chemical-specific data submitted by DAS, the remaining scenarios were evaluated using the Residential SOPs or PHED.

The results of the **residential postapplication** exposure scenarios indicate that **seven of the nine** scenarios evaluated have MOEs that are less than 1000, and therefore **exceed HED's level of concern**. These scenarios include exposures following indoor crack and crevice treatment, pet collars, termiticide treatments, liquid and granular lawn treatments and yard and ornamental sprays. In addition, for post application exposure to children following perimeter applications to homes, it was estimated that more than seven hand-to-mouth events or more than 8 minutes of play on treated turf the day of treatment could result in potential exposures that could exceed the Agency's level of concern (i.e., MOE < 1000). An additional scenario could not be quantitatively evaluated (post application exposure to insecticidal dust product use) due to an absence of chemical-specific data and recommended procedures in the residential SOPs. MOEs that exceed HED's level of concern ranged from 6 to 980 for total dermal, inhalation and inadvertent oral (in the case of children) risk. The only residential/recreational scenarios that resulted in a MOE above 1000 are the aerial and ground-based fogger adult mosquitocide application (MOEs 15,000 to 42,000) and adolescent and adult golfers for the typical application rate of 1 lb ai/acre (MOEs 1500 - 2400). Several of the residential postapplication risks were estimated based on chemical-specific studies submitted by DAS (i.e., crack and crevice treatment of the kitchen and bathroom, broadcast treatment of turf with chlorpyrifos spray or granules, and termiticide treatment). The exposure and risk estimates based on the chemical-specific studies are considered to be reasonable central-tendency estimates (i.e., arithmetic mean or median exposure was used to calculate risk). Because these studies were conducted in adults, standard EPA assumptions were used to estimate child exposures.

Poisoning Incidents

Because of its widespread use in residences, chlorpyrifos is often involved in unintentional exposures. About 6% of all pesticide-related calls (estimated at 7,000 annually) received by the poison control centers are related to chlorpyrifos. The overwhelming majority of cases experience only minor symptoms, but about 200 cases per year are serious enough to require special medical attention. Although only a small proportion of cases involve products used by pest control operators, these exposures often involve exposures to concentrated chemical, which can lead to more serious health effects.

Aggregate Exposure and Risk

As mandated by the FQPA amendments to the Federal Food, Drug and Cosmetic Act (FFDCA), the Agency must consider total aggregate exposure from food, drinking water, and residential sources of exposure to chlorpyrifos. Based on the mitigation plan, this aggregate assessment considers exposure to chlorpyrifos from food, drinking water and residential uses. In addition, the Agency has concerns about possible residential exposures from chlorpyrifos spray drift. The Agency is currently developing methods to

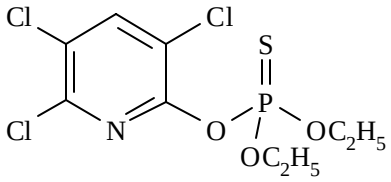
assess residential exposures from spray drift, and these will be assessed in the future when new methods are available. The **acute aggregate risk estimates do not exceed HED's level of concern** because combined exposure to chlorpyrifos through food and drinking water sources are <100% aPAD. The **short-term aggregate risk estimates do not exceed HED's level of concern** based on concurrent exposure to chlorpyrifos from golfing, mosquito abatement activities, in addition to food and drinking water. The **chronic** food and drinking water **aggregate risk estimates do not exceed HED's level of concern**.

Although not all of the risk estimates for termiticide use achieve a margin of exposure of 1000, the Agency believes that individuals are unlikely to experience adverse health effects from the termiticide use of chlorpyrifos. This conclusion is based on: the public health protective assumptions; the 1000 fold safety factor; and the additional 3 to 10 fold cushion between the NOAEL and the LOAEL. Mitigation measures will further reduce exposures and risk associated with the termiticide use. For example, the removal of whole house barrier treatment addressed the exposures of most concern. It is expected that the limited spot and localized treatment, and pre-construction treatments would represent less exposure and risk. In conclusion, based on the mitigation plan, and best professional and scientific judgement, the Agency concludes that the chronic aggregate risk including termiticide use, does not raise a concern.

Because of its extensive use, the majority of the U.S. population is exposed to chlorpyrifos or its environmental breakdown product, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP). Epidemiology data have reported measurable concentrations of 3,5,6-TCP, which is also the primary metabolite of chlorpyrifos, chlorpyrifos-methyl and trichlorpyr in the urine of individuals. These data represent potential aggregate exposure to chlorpyrifos and/or 3,5,6-TCP from all exposure routes. 3,5,6-TCP was detected in the urine of 82% of 993 adults from the National Health and Nutrition Examination Survey III conducted between 1988 and 1993 (NHANES III). Preliminary results from the recent Minnesota Children's Exposure Study found that 92% of the 89 children evaluated had measurable urinary concentrations of 3,5,6-TCP. A 1998 biomonitoring study of 416 children in North and South Carolina found 3,5,6-TCP in urine of 100% of the children evaluated. TCP was found at higher average levels than all previous epidemiological studies of the general population. HED believes that chlorpyrifos contributes significantly more to urinary TCP than chlorpyrifos-methyl and trichlorpyr based on relative usage of 21-24 million pounds chlorpyrifos versus 92,000 pounds chlorpyrifos-methyl, and 700,000 pounds for trichlorpyr. Because chlorpyrifos, chlorpyrifos-methyl and trichlorpyr degrade to 3,5,6-TCP in the environment, exposure to TCP per se also contributes to the urinary 3,5,6-TCP residues to an unknown degree. As noted previously, HED conducted a screening-level risk assessment for TCP. This assessment is attached in memorandum from S. Knizner to D. Smegal, D265035 June 5, 2000.

2.0 Physical/Chemical Properties Characterization

Technical chlorpyrifos is a white crystalline solid with a melting point of 41.5-42.5° C. Chlorpyrifos is stable in neutral and acidic aqueous solutions; however, stability decreases with increasing pH. Chlorpyrifos is practically insoluble in water, but is soluble in most organic solvents (i.e., acetone, xylene and methylene chloride). Chlorpyrifos is not particularly volatile based on its low vapor pressure of 1.87×10^{-5} mmHg at 20°C (Merck Index, 11th Edition). Its maximum attainable vapor concentration is 25 ppb at 25° C.



Empirical Formula:	$C_9H_{11}Cl_3NO_3PS$
Molecular Weight:	350.6
CAS Registry No.:	2921-88-2
Chemical No.:	059101

The persistence of chlorpyrifos in soil varies depending on soil type, and environmental conditions. The typical aerobic soil metabolism half life ($T_{½}$) ranges from 11 to 180 days, with a mean of 28.7 days. Much longer soil half lives of 175 to 1576 days have been reported for termiticide application rates (Memorandum from M. Barrett to S. Knizner, Drinking Water Assessment of Chlorpyrifos, November 13, 1998, and memorandum from H. Nelson to D. Smegal/M. Hartman, October 6, 1999). The soil/water partition coefficient (K_{oc}) value ranges from 360 to 31000, indicating that it is not very mobile in soils.

Technical Grade Active Ingredient (TGAI) data requirements concerning the DAS 99% T (EPA Reg. No. 62719-44) and the 97% T (EPA Reg. No. 62719-15) are satisfied. Guideline 830.6314 (oxidatioin/reduction) data requirements remain outstanding for the DAS 99% T. There are 45 chlorpyrifos Manufacturing-Use Products (MPs). Data remain outstanding for many MPs. Product chemistry data requirements will be complete, provided that the registrants submit the data required as identified in the Revised Product and Residue Chemistry Chapter (Memorandum from S. Knizer to M. Hartman, October 1, 1999, D259613) for the chlorpyrifos MPs. In addition, the registrants must either certify that the suppliers of starting materials and the manufacturing processes for the chlorpyrifos technicals and manufacturing-use products have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages.

3.0 Hazard Characterization

3.1 Hazard Profile

The toxicological database is complete and adequate to support reregistration. in accordance with the Subdivision F Guidelines for a food use chemical.

Chlorpyrifos is moderately toxic following acute oral, dermal and inhalation exposures and is classified in toxicity category II for all exposure routes. Chlorpyrifos affects the nervous system by reversibly inhibiting the activity of cholinesterase (ChE), an enzyme necessary for the proper functioning of the nervous system. Inhibition of ChE is the most sensitive effect in all animal species evaluated and in humans, regardless of exposure duration. In animals, significant inhibition of plasma and red blood cell (RBC) ChE occur at doses below those that cause brain ChE inhibition. In animals, significant plasma and RBC ChE have been observed at oral doses as low as 0.025 to 0.3 mg/kg/day following exposure for two weeks to two years, while significant brain ChE inhibition has been observed at oral doses as low as 1 mg/kg/day following exposure for two weeks in pregnant rats (Hoberman 1998a,b). Female rats and especially pregnant rats appear to be more sensitive than adult male rats to cholinesterase inhibition (Moser et al. 1998, Hoberman 1998a,b, Mattsson et al. 1998). Data from two human studies suggest that humans (adult males) are similarly sensitive and possibly more sensitive than rats and dogs following acute and short-term oral exposure and acute dermal exposure based on plasma ChE inhibition and/or possible clinical signs. It is likely that the human sensitivity for ChE inhibition relative to rats (but not dogs) is due to species differences in the constituents of plasma ChE between rats and humans. For example, in rats, plasma ChE consists of approximately a 60:40 ratio of acetyl cholinesterase (AChE) and butyryl cholinesterase (BuChE), while in most humans and dogs, plasma ChE is predominately as BuChE, which is more sensitive to inhibition than AChE.

3.1.1 TCP

HED has concluded that the primary metabolite of chlorpyrifos, 3,5,6-trichloro-2-pyridinol (3,5,6-TCP), does not induce cholinesterase inhibition, and therefore is less toxic than chlorpyrifos (58 FR 19354, April 14, 1993). However, because of the potential exposure to TCP in food and residential settings, and evidence of increased susceptibility of rabbit fetuses relative to dams, HED conducted a screening-level risk assessment for TCP. This assessment is attached in a memorandum from S. Knizner to D. Smegal, D265035 June 5, 2000.

3.1.2 Neurotoxicity

Adult male rats acutely exposed to chlorpyrifos exhibited peak plasma ChE inhibition of 28-40% 3-6 hours after exposure at 1 mg/kg (Mendrala and Brzak 1998), while significant 30% RBC ChE inhibition was noted 4 hours following a single oral dose of 1.5 mg/kg (Zheng et al. 2000). Plasma, RBC and heart ChE inhibition of 45%, 17% and 19%, respectively were observed in female rats 24 hours following a single dose of 5 mg/kg (Dittenber 1997). The acute oral NOAEL for plasma ChE inhibition in male rats is 0.5 mg/kg/day. Clinical signs of neurotoxicity, in the absence of neuropathology, were observed in rats exposed to a single oral dose of 50 mg/kg as evidence by decreased motor activity, and increased incidence of clinical signs consistent with organophosphate intoxication. Chlorpyrifos was negative in the delayed neurotoxicity study in hens at single doses of 50, 100 or 110 mg/kg. Acute oral exposure to hens at 60 to 150 mg/kg caused 59-87% inhibition of neurotoxic esterase (NTE) 4-6 days after exposure (Capodicasa et al. 1991). In addition, delayed neuropathy was noted at 60-90 mg/kg which corresponded to 4-6 times the LD_{50} and required aggressive antidotal treatment. In rats, chlorpyrifos failed to inhibit NTE at single doses up to 100 mg/kg. There is evidence that NTE inhibition is related to organophosphate-induced delayed neuropathy (OPIDN).

Following longer-term exposures, there was no evidence of neurotoxicity or neuropathology in rats exposed at doses up to 15 mg/kg/day for 13 weeks. However, in the developmental neurotoxicity study, pregnant dams exposed to chlorpyrifos for approximately 2 weeks exhibited 43% and 41% inhibition of plasma and RBC ChE activity at 0.3 mg/kg/day, significant 18% brain ChE inhibition at 1 mg/kg/day, and clinical signs of neurotoxicity, including fasciculations (muscle twitching), hyperpnea (increased respiration), and hyperactivity in addition to decreased body weight gain at 5 mg/kg/day (Hoberman 1998a,b). Cholinesterase inhibition (68% plasma, 56% RBC and 8% brain) was also noted in rats exposed to 1 mg/kg/day chlorpyrifos for 4 weeks in the cognitive study, while clinical signs of toxicity were not observed until higher doses of 3 mg/kg/day for miosis (pupil contraction) and 10 mg/kg/day for salivation and tremors (Maurissen et al. 1996).

3.1.3 Subchronic Toxicity

Several subchronic studies are available for chlorpyrifos including two oral rat studies, one oral dog study, a 21 day dermal toxicity study in rats, and two inhalation studies in rats. The most sensitive effect following subchronic oral exposure is inhibition of plasma ChE in rats and dogs at 0.025 to 0.03 mg/kg/day, and RBC ChE inhibition in dogs and rats at 0.22 to 0.3 mg/kg/day. Rats exposed to higher doses exhibited hematological

effects at doses of 10 mg/kg/day and increased brain and heart weight, adrenal gland effects and decreased body weight gain at 15 mg/kg/day. No adverse effects were noted in rats exposed via inhalation to the highest attainable vapor concentration of 20.6 ppb (287 Fg/m^3) (0.1 mg/kg/day). No adverse effects were observed in the 21-day dermal study in rats at doses as high as 5 mg/kg/day. However, in a 4-day dermal probe study, rats dermally exposed to doses of 0, 1, 10, 100, or 500 mg/kg/day exhibited reductions in plasma and RBC ChE activities at doses of 10 to 500 mg/kg/day. The 21-day dermal NOAEL is 5 mg/kg/day based on a 45% and 16% inhibition of plasma and red blood cell cholinesterase, respectively in rats dermally exposed to 10 mg/kg/day for 4 days.

3.1.4 Carcinogenicity/Genotoxicity

Chlorpyrifos was evaluated for carcinogenic potential in both rats (2 studies), and mice (2 studies). There was no evidence of carcinogenicity. Chlorpyrifos is not mutagenic in bacteria, or mammalian cells, but did cause slight genetic alterations in yeast and DNA damage to bacteria. In addition, chlorpyrifos did not induce chromosome aberrations in vitro, was not clastogenic in the mouse micronucleus test in vivo, and failed to induce unscheduled DNA synthesis in isolated rat hepatocytes.

3.1.5 Chronic Toxicity

Chlorpyrifos was evaluated for chronic toxicity in rats, mice and dogs. In all animal species, the most sensitive effect is inhibition of plasma, RBC and brain ChE that occurred at levels in the range of 0.03 to 3 mg/kg/day. Following chronic exposure dogs appear to be the most sensitive species for cholinesterase inhibition and systemic effects, as noted by increased liver weights in dogs exposed to 3 mg/kg/day that could be an adaptive response. Rats exposed to 7-10 mg/kg/day had decreased body weight and decreased body weight gain, ocular effects, adrenal gland effects and altered clinical chemistry and hematological parameters. Mice appear to be the least sensitive to chronic oral doses of chlorpyrifos, as exposure to 45-48 mg/kg/day resulted in decreased body weight and an increased incidence of non-neoplastic lesions (i.e., keratitis, hepatocyte fatty vacuolation).

3.1.6 Developmental Toxicity

Chlorpyrifos was evaluated for developmental toxicity in rats, mice and rabbits. In one rat study, developmental effects (increased post-implantation loss) were noted at 15 mg/kg/day (highest dose tested, HDT), that were also associated with maternal toxicity, while another rat study failed to observe developmental effects at 15 mg/kg/day. Developmental effects were also noted at higher doses in mice at 25 mg/kg/day (minor skeletal

variations, delayed ossification and reduced fetal weight and length) and rabbits at 140 mg/kg/day (decreased fetal weights and crown rump lengths, and unossified xiphisternum and/or 5th sternebra). However, in both mice and rabbits, the developmental effects occurred at maternally toxic doses as indicated by reduced weight gain, and food consumption in both species, and increased mortality in mouse dams.

In the rat developmental neurotoxicity study, chlorpyrifos was associated with delayed alterations in brain development in offspring of exposed mothers. Specifically, pups of the 1 mg/kg/day group exhibited significant dose- and treatment-related decreases in measurements of the parietal cortex in female offspring at postnatal day 66. The only maternal effect at this dose was plasma and RBC ChE inhibition. At higher doses, pups of the 5 mg/kg/day group exhibited decreased body weight/body weight gain and food consumption in both sexes, reductions in pup viability, delays in development, decreased brain weight and morphometric alterations in the brain. However, these effects were observed in the presence of maternal toxicity as evidenced by fasciculations, hyperpnea and hyperactivity, in addition to reduced body weight gain.

Several studies in the peer reviewed literature and results of the guideline developmental neurotoxicity study are supportive of the possibility that chlorpyrifos exposure may affect brain development (e.g., altered synaptic development, alterations in DNA, RNA, and protein synthesis, inhibition of mitosis and mitotic figures, and disruption of the structural architecture of the brain) (Whitney et al. 1995, Campbell et al. 1997, Song et al. 1997, Johnson et al. 1998, Das and Barone 1999, Dam 1999, Roy et al. 1998, Hoberman 1998a,b). There are suggestive data that these effects may arise independent of cholinesterase inhibition.

3.1.7 Reproductive Toxicity

Chlorpyrifos induced reproductive toxicity in one generation of rats, but only at dose levels that induced parental toxicity. Reproductive effects included reduced pup weights and increased pup mortality that corresponded to slightly but significantly reduced body weight gain in F0 dams during lactation days 1-21, in addition to parental toxicity as evidenced by inhibition of plasma, RBC and brain cholinesterase activities as well as histological lesions of the adrenal gland (vacuolation of cells of the zona fasciculata).

3.1.8 Human Studies

HED has reviewed two human studies conducted with chlorpyrifos submitted by the registrant (MRID 95175, Accession No. 249203). A third

human study (Kisicki et al. 1999) that evaluated a single dose exposure was submitted on April 27, 1999 but is an incomplete submission because two Appendices with critical data were omitted. In the first study (MRID No. 95175; Coulston et al., 1972), male volunteers from Clinton Correctional Facility (4/dose group) were given daily oral (tablet) doses of 0, 0.014, 0.03, or 0.1 mg/kg chlorpyrifos technical for 7 weeks, 9 days, 21 days and 28 days, respectively. Significant 36-82% plasma ChE inhibition relative to baseline was observed after 9 days of treatment with 0.1 mg/kg/day chlorpyrifos. In addition, one of the four men in the 0.1 mg/kg/day developed blurred vision, runny nose and a feeling of faintness on day 9. Exposure was discontinued on day 9 in this dose group however, due to plasma cholinesterase inhibition that exceeded the study investigator's guideline of 20%-30%. No significant plasma ChE inhibition was observed in the men exposed to 0.03 mg/kg/day for 21 days or at any other dose that could be attributed to treatment. No effects on RBC ChE were found at any dose that could be attributed to treatment. A gradual recovery was observed in plasma ChE values equaling baseline values by day 25 of the recovery period. The registrant and study director contend that the clinical signs were attributed to a cold, and not chlorpyrifos exposure. HED believes that blurred vision is a typical cholinergic sign of ChE inhibition, and can not be attributed to a common cold (February 2, 1998 HIARC Report, HED Doc No. 012471). In addition, there is no reason to believe that other clinical signs would not have appeared if the dosing had continued for 21 or 28 days as it did for the other groups. While the study director claims that exposure to the high dose group was discontinued on day 9 because plasma ChE inhibition was 20-30%, rather than because of concern for the clinical signs, this reason is inconsistent with the study findings of 46% mean plasma ChE inhibition following day 6 of treatment in the 0.1 mg/kg/day group, and 41% plasma ChE inhibition in one individual on day 3. HED notes that the relatively long recovery period of 25 days is unusual for plasma ChE, and is more characteristic of recovery for RBC acetyl ChE inhibition based on the 2 year dog data (McCollister et al. 1971, Kociba et al. 1985).

An acute oral and dermal pharmacokinetic study (Nolan et al. 1982, Accession No. 249203) dosed six men once with 0.5 mg/kg orally and four weeks later dosed five of these same men with 5 mg/kg dermally, and one man with 0.5 mg/kg dermally. No clinical signs or symptoms were observed in any of the subjects, but unlike the previous study, the primary focus of this study was pharmacokinetics. Men orally exposed to 0.5 mg/kg chlorpyrifos exhibited peak plasma ChE inhibition of 64-85%, 12 to 24 hours post-exposure. Peak RBC ChE inhibition of 11-52% occurred on post-exposure day 4. Men dermally exposed to 5 mg/kg chlorpyrifos exhibited peak plasma ChE inhibition of 27-45% on day 3, and mean RBC ChE inhibition of 8.6% on day 4. The return of plasma ChE activity to pre-dose levels required about 30 days. The registrant stated that the inhibition noted on days 3 and 4 is an analytical artifact based on chlorpyrifos

pharmacokinetics. If this is the case, it raises concerns about the quality and reliability of the study data. Again, HED notes that the relatively long recovery period of 30 days is unusual for plasma ChE, and is more characteristic of recovery for RBC acetyl ChE inhibition based on the 2 year dog data (McCollister et al. 1971, Kociba et al. 1985). On the basis of urinary excretion of the 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) metabolite, the minimum oral absorption of chlorpyrifos was estimated at 70% and the minimal dermal absorption at 1-3%. Because the proportion of the administered dose metabolized to this pyridinol is unknown, these estimates are considered minimum values (i.e., absorption could be higher). The mean pharmacokinetic half-life for 3,5,6-TCP in the urine was approximately 27 hours following both oral and dermal exposure.

As noted previously, data from the two human studies suggest that humans are as sensitive and possibly more sensitive than animals based on plasma ChE inhibition and possible clinical signs. For example, in animals (rats), the acute oral (single dose) NOAEL is 0.5 mg/kg/day, while humans exposed to a single oral 0.5 mg/kg/day dose exhibited 64-85% plasma ChE inhibition. Based on an overall assessment of the plasma and RBC ChE inhibition data, the HIARC identified an animal NOAEL and LOAEL of 0.03 mg/kg/day and 0.22-0.3 mg/kg/day, respectively for longer term exposures (several months), while humans exposed to 0.1 mg/kg/day for only 9 days exhibited 36-82% plasma ChE inhibition and possible clinical signs (blurred vision). The short-term dermal NOAEL in rats is 5 mg/kg/day based on plasma and RBC ChE inhibition observed at 10 mg/kg/day, while humans exposed dermally for one day to 5 mg/kg/day exhibited 27-45% plasma ChE inhibition. For all endpoints based on rat data, it is likely that this sensitivity can be attributed to species differences in plasma ChE between the rat and humans. For example, in rats, plasma ChE consists of approximately a 60:40 ratio of acetyl cholinesterase (AChE) and butyryl cholinesterase (BuChE), while in most humans and dogs, plasma ChE is predominately as BuChE, which is more sensitive to inhibition than AChE.

3.1.9 Metabolism/Pharmacokinetic Studies.

In the rat, chlorpyrifos is excreted primarily in the urine (84%) with lesser amounts excreted in the feces (5%) within 72 hours. The metabolism of chlorpyrifos was extensive, and no unchanged parent compound was found in the urine. The major urinary metabolites were 3,5,6-TCP, as well as glucuronide and sulfate conjugates of TCP.

As noted previously, in humans (adult males) approximately 70% of chlorpyrifos is excreted in the urine as TCP within 5 days following acute oral exposure, and the minimum dermal absorption is 1 to 3% (Nolan et al. 1982, Accession No. 249203). The mean pharmacokinetic half-life for 3,5,6-TCP in the urine was approximately 27 hours following both oral and dermal

exposure.

3.1.10 Sensitivity/Susceptibility of the Young

A number of studies published in the scientific literature have also been considered by the Agency and are discussed in the Hazard Identification and Assessment Review Committee (HIARC) April 6, 2000 report (HED No. 014088), February 2, 1998 report (HED No. 012471) and December 7, 1998 report (HED No. 013004). Summaries of several of these studies are presented in the attached Toxicology Chapter memorandum from D. Smegal to M. Hartman, April 18, 2000, D263892, and in the report "Chlorpyrifos Children's Hazard: Sensitivity and Susceptibility" March 28, 2000, HED No. 014074 (which is an appendix to the April 6, 2000 HIARC report). The HIARC concluded that there is sufficient evidence in the scientific literature to suggest that exposure to chlorpyrifos results in increased sensitivity and susceptibility to neonates as compared to adult rats. The Weight of Evidence Characterization and Conclusions of the "Chlorpyrifos Children's Hazard: Sensitivity and Susceptibility" document (March 28, 2000, HED No. 014074) are presented in Appendix A.

3.1.11 Paraoxonase

Chlorpyrifos, and some other organophosphate (OP) compounds, are detoxified via a two-step pathway involving bioactivation of the parent compound to an oxon by the cytochrome P450 systems, and then hydrolysis of the resulting oxon compounds by esterases such as liver or serum paraoxonase (PON1) (located in the plasma) (Davies et al. 1996, Furlong et al. 1998, Shih et al. 1998). In the human population, serum PON1 activity is genetically determined (polymorphic) and individuals express widely different levels of this enzyme (Davies et al. 1996). Therefore, it is possible that some individuals may be more sensitive to chlorpyrifos toxicity based on genetic factors that regulate serum PON1 activity resulting in a reduced capacity to detoxify chlorpyrifos-oxon. Paraoxonase data were collected for individuals in a recent single dose human study (Kisicki et al. 1999). HED will evaluate these data once they are submitted to the Agency.

In animals, there is evidence that serum paraoxonase is protective against poisoning by OPs. Animals with low PON1 levels were more sensitive to specific OP compounds than animals with high enzyme levels. For example, birds, which have very low to undetectable PON1 activity are more sensitive than various mammals to the acute toxicity of oxons for other OPs (paraoxon, diazinon oxon and pirimiphos oxon). Further rabbits, which have a sevenfold higher serum PON1 activity than rats, are more resistant to the acute toxicity of chlorpyrifos (approximately 9 and 25 fold for acute oral and dermal toxicity, respectively). Rabbit paraoxonase hydrolyzes chlorpyrifos-oxon with a much higher turnover number than does rat paraoxonase (Costa et al. 1999, Li et al. 1993).

3.2 Acute Toxicity

Chlorpyrifos is moderately toxic following acute oral, dermal and inhalation exposures, and is classified in toxicity category II for all three routes of exposure for rats. The oral LD_{50} values for technical chlorpyrifos are higher in rats (223 mg/kg) than mice (62.5 mg/kg, toxicity category II) or chicks (32 mg/kg, toxicity category 1). Female rats are more sensitive (i.e., lower LD_{50}) than male rats for both technical chlorpyrifos and formulated products. Guinea pigs and rabbits are less sensitive to acute toxicity than rats as noted by the oral LD_{50} values of 504 mg/kg and 1000-2000 mg/kg, respectively (both category III), and the rabbit dermal LD_{50} value of >5000 mg/kg (category IV). Chlorpyrifos was not acutely neurotoxic when given to hens at a single oral dose of 50 mg/kg (the LD_{50}), 100 or 110 mg/kg. In rats, the LC_{50} was greater than 0.2 mg/L (or 200 mg/m^3), which is normally assigned toxicity category II. This study is classified as Supplementary because only nominal concentrations were measured. Acute toxicity values and categories for the technical grade of chlorpyrifos are summarized in the following table.

Table 1. Acute Toxicity Results for Technical Chlorpyrifos

STUDY	MRID Number	RESULTS	CATEGORY
Acute Oral LD_{50} - rat	44209101	223 mg/kg M&F	II
Acute Dermal LD_{50} - rat	Accession No. 112115	202 mg/kg	II
Acute Dermal LD_{50} - rabbit	44209102	>5000 mg/kg	IV
Acute Inhalation LC_{50}; rat Supplementary	00146507 and Accession No. 257590	LC_{50} > 0.2 mg/L (200 mg/m^3) (nominal concentration)	II
Eye Irritation - rabbit	44209103	slight irritation resolved within 24 hours	IV
Dermal Irritation - rabbit	44209104	mild irritant; (irritation resolved within 7 days)	IV
Dermal Sensitization - guinea pig	44209105	non-sensitizing	NA
Acute Delayed Neurotoxicity in hens	00097144 00405106	not neurotoxic at 50, 100 or 110 mg/kg	NA

NA = not applicable

3.3 FQPA Considerations

In March 1999, the FQPA Safety Factor Committee (SFC) recommended that an FQPA safety factor was needed due to concern for increased sensitivity seen at high doses in a literature study comparing adults and neonates, and for the qualitative increased susceptibility occurring at the high dose in the developmental neurotoxicity study. Nonetheless, the FQPA safety factor was reduced to 3X because of lack of data addressing whether or not these differences would also occur at lower doses. A re-evaluation of this recommendation was conducted by the FQPA SFC on January 24, 2000. The new evaluation was undertaken in order to consider the possible impact of new hazard information received in the last year (Slotkin 1999, Zheng et al. 2000). At the January 24th meeting, however, the Committee members were unable to reach consensus on the safety factor recommendation. Subsequently, arguments for retention of the safety factor at 10X or reduction of the safety factor to 3X were presented, with supporting information for review, to the OPP Division Directors and several Agency senior scientists at a February 7, 2000 meeting. The Division Directors and senior scientists (DD-SS group), recommended that the FQPA safety factor should be **retained at 10X** for the protection of infants and children to exposure resulting from chlorpyrifos. The details of this decision are presented in the attached memo from B. Tarplee 4/4/00 HED Doc No. 014077. The DD-SS group recommended that a 10X safety factor be retained for chlorpyrifos due to:

In February 2000, new data (Zheng et al. 2000, Hoberman 1998a,b) demonstrated that the increased sensitivity and susceptibility was not only a high dose phenomenon since:

< increased sensitivity following a single oral exposure to neonates was seen at substantially lower doses (Zheng et al. 2000, in press); and

< a clear qualitative difference in response (i.e., susceptibility) between adult rats and their offspring was demonstrated in the developmental neurotoxicity (DNT) study (cholinesterase inhibition in dams versus structural effects on developing brain of the offspring) (Hoberman 1998a,b).

New data in the literature also gave rise to uncertainties such as:

< the suggestion that the inhibition of cholinesterase may not be essential for adverse effects on brain development; and

< the lack of an offspring NOAEL in the DNT based upon structural alterations in brain development as the toxicity endpoint of concern.

Therefore, the DD-SS group concluded that their evaluation of the available hazard and exposure databases for chlorpyrifos, including the information received and

reviewed in the past year, results in an overall ***higher*** degree of concern regarding the potential consequences of chlorpyrifos exposure to infants and children than was determined during the FQPA safety factor evaluation in March 1999. Consequently, they recommended that the FQPA safety factor should be Retained at 10X for the protection of infants and children to exposure resulting from the use of chlorpyrifos.

The FQPA SFC determined that the FQPA safety factor would be applicable to **Females 13-50** and **Infants and Children** population subgroups for **all exposure durations**:

Acute Dietary Assessment - The FQPA safety factor is applicable for Females 13-50 and Infants and Children population subgroups due to the concern that adverse effects could result from a single exposure to chlorpyrifos (as demonstrated in several open literature studies including Zheng et al.).

Chronic Dietary Assessment - The FQPA safety factor is applicable for Females 13-50 and Infants and Children population subgroups due to the concern that potential adverse effects could result from repeated exposure to chlorpyrifos (as demonstrated, for example, in the developmental neurotoxicity study in rats).

Residential and other Non-occupational Exposure Assessment - The FQPA safety factor is applicable for Females 13-50 and the Infants and Children population subgroups for all exposure durations due to the adverse effects resulting from single or repeated exposure(s) to this organophosphate insecticide in or around residential (non-occupational) settings.

3.4 Endpoint Selection

It is current Agency policy that a regulatory decision can not be made based on a human study until a formal decision has been made concerning the ethical aspects of such use. The ethics decision regarding the use of toxicology studies employing human subjects has not yet been made. Therefore, the Agency selected doses and endpoints to calculate dietary and non-dietary risk in the current assessment based solely on animal studies.

There are three human studies available for chlorpyrifos, however one of these studies is an incomplete submission (Kisicki et al. 1999). The HED HIARC met on January 5, 1999 to evaluate the scientific quality of the two human studies which were the basis of the previous RfDs and dermal and inhalation risk assessment endpoints. This re-evaluation was initiated because of a joint Science Advisory Panel/Science Advisory Board (SAP/SAB) meeting held in December 1998 that discussed issues surrounding the scientific and ethical concerns for human toxicity testing. The HIARC committee concluded that both human studies (Coulston et al. 1972 MRID No. 00095175, Nolan et al. 1982, MRID No. 00249203)

provided useful scientific information that can be used as supportive data along with the results of animal studies. However, these studies alone are not sufficient for endpoint selection or use in risk assessment primarily because of the small sample size (n=4-6/dose group), evaluation of only adult males (when females tend to be more sensitive), insufficient information on study protocol, and lack of control for confounding factors. In addition, the Nolan et al. (1982) pharmacokinetic study only tested one dose level. Furthermore, the registrant contends that the plasma and RBC ChE activity data results on day 3 and 4 of the Nolan et al. (1982) study are analytical artifacts, which raises concerns about the quality and reliability of the study data.

The HIARC met on February 2, 1999 and re-assessed the toxicology database to select toxicology endpoints based on animal studies for dietary and non-dietary exposure risk assessments. On January 20, 2000, and March 28, 2000 the Committee re-convened to address issues raised during the Phase 3 public comment period. The Committees decisions are presented in the attached HIARC memorandum dated April 6, 2000 (D. Smegal to S. Knizner, HED Doc No. 014088). The doses and toxicological endpoints selected for various exposure scenarios based on animal toxicity studies with chlorpyrifos are summarized in Table 2.

Table 2
Summary of Doses and Endpoints Selected for Chlorpyrifos Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	Target MOE for Workers	Target MOE for Non-Occupational
Acute Dietary	NOAEL=0.5 UF = 100 FQPA = 10 (infants,children and females 13-50)	Significant (28-40%) plasma cholinesterase inhibition at peak time of inhibition (3-6 hours post exposure) at 1 mg/kg (Mendrala and Brzak 1998). Significant 30% RBC ChE inhibition 4 hours post exposure to 1.5 mg/kg/day (Zheng et al. 2000).	Acute Blood Time Course Study in male rats (Mendrala and Brzak 1998) with support from Zheng et al. (2000)	NR	NR
	Acute RfD =0.005 mg/kg/day **Acute PAD (children and females 13-50) = 0.0005 or $5x10^{-4}$ mg/kg/day** **Acute PAD (general population) = 0.005 or $5x10^{-3}$ mg/kg/day**				
Chronic Dietary	NOAEL= 0.03 UF= 100 FQPA = 10 (infants,children and females 13-50)	Significant plasma and RBC cholinesterase inhibition at 0.22 to 0.3 mg/kg/day	Weight of Evidence from 5 studies: 2 year dog 90 day dog 2 year rat 90 day rat developmental neurotoxicity (DNT) study (at 2 weeks)	NR	NR
	Chronic RfD =0.0003 mg/kg/day **Chronic PAD (children and females 13-50) = 0.00003 or $3x10^{-5}$ mg/kg/day** **Chronic PAD (general population) = 0.0003 or $3x10^{-4}$ mg/kg/day**				
Short-Term (Dermal)	Dermal NOAEL =5 Absorbed Dermal NOAEL = 0.15 (for biomonitoring) (a)	Plasma and RBC cholinesterase inhibition of 45 and 16%, respectively at 10 mg/kg/day after 4 days. (Dermal absorption factor not necessary for administered dermal NOAEL)	21-day dermal rat study	100	1000 (infants,children and females 13-50) 100 (males)

Table 2
Summary of Doses and Endpoints Selected for Chlorpyrifos Risk Assessment

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY	Target MOE for Workers	Target MOE for Non-Occupational
Intermediate- and Long-Term (Dermal)	Oral NOAEL =0.03 (3% dermal absorption)	Significant plasma and RBC cholinesterase inhibition at 0.22 to 0.3 mg/kg/day	Weight of Evidence from 5 studies: 2 year dog 90 day dog 2 year rat 90 day rat DNT study (at 2 weeks)	100	1000 (infants,children and females 13-50) 100 (males)
Short-,and Intermediate-Term (Inhalation)	Inhalation NOAEL= 0.1	Lack of effects in 2 rat inhalation studies at the highest dose tested; 43% plasma and 41% RBC cholinesterase inhibition following oral doses of 0.3 mg/kg/day for 2 weeks in the DNT study	Two 90 day rat inhalation studies (NOAEL) and DNT (LOAEL)	100	1000 (infants,children and females 13-50) 100 (males)
Long-Term (Inhalation)	Oral NOAEL= 0.03 (assume inhalation absorption is 100% of oral absorption)	Significant plasma and RBC cholinesterase inhibition at 0.22 to 0.3 mg/kg/day	Weight of Evidence from 5 studies: 2 year dog 90 day dog 2 year rat 90 day rat DNT (at 2 weeks)	100	1000 (infants,children and females 13-50) 100 (males)

RBC = red blood cell
NR = not relevant
UF = Uncertainty Factor
MOE = Margin of Exposure
PAD = Population Adjusted Dose (includes UF and FQPA safety factor)
(a) Use absorbed dermal NOAEL of 0.15 mg/kg/day (5 mg/kg/day * 0.03 dermal absorption factor) for comparison with absorbed biomonitoring exposure.

3.5 Endocrine Disrupter Effects

The Food Quality Protection Act (FQPA; 1996) requires that EPA develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect...." EPA has been working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists to develop a screening and testing program as well as a priority setting scheme to implement this program. The Agency's proposed Endocrine Disrupter Screening Program was published in the Federal Register of December 28, 1998 (63 FR71541). The Program uses a tiered approach and anticipates issuing a Priority List of chemicals and mixtures for Tier 1 screening in the year 2000. As the Agency proceeds with implementation of this program, further testing of chlorpyrifos and its end-use products for endocrine effects may be required.

4.0 Exposure Assessment

4.1 Summary of Registered Uses

Chlorpyrifos is a broad-spectrum, organophosphate insecticide that was first registered in 1965 to control foliage- and soil-borne insect pests on a variety of food and feed crops. It is one of the most widely used organophosphate insecticides in the U.S. and is one of the major insecticides used in residential settings. There are approximately 822 registered products containing chlorpyrifos on the market (REFs 9/14/99). Registered uses include: a wide variety of food crops (i.e., there are approximately 112 tolerances for food and/or feed commodities such as citrus, vegetable crops, tree fruits, etc); turf and ornamental plants; greenhouses; sodfarms; indoor pest control products (e.g., crack and crevice); structural pest control (e.g., termites); and in pet collars. Indoor uses include residential and commercial buildings, schools, daycare centers, hotels, restaurants and other food handling establishments, hospitals, stores, warehouses, food manufacturing plants, vehicles, livestock premises, and mushroom houses. In addition, it is used as an adult mosquitocide and is registered for ear tag treatment of cattle (beef and lactating and non-lactating dairy). Chlorpyrifos products are widely used by both homeowners and LCOs/PCOs.

BEAD estimates that the annual total domestic usage of chlorpyrifos is approximately 21 to 24 million pounds ai for 8 million acres treated in the U.S. Approximately 11 million pounds are applied annually in non-agricultural settings (i.e., residences, schools, golf courses, parks). Chlorpyrifos has the largest agricultural market in terms of total pounds ai allocated to corn (26%). The largest non-agricultural markets in terms of total pounds ai applied are PCOs, termite control (24%), and turf (12%). Crops with a high average percentage of their total

U.S. planted acres treated include brussel sprouts (73%), cranberries (46%), apples (44%), broccoli (41%) and cauliflower (31%).

Comprehensive lists of chlorpyrifos end-use products (EPs) and of use patterns with food/feed uses which are subject to re-registration appear are summarized in the Revised Product and Residue Chapter (Memorandum from S. Knizner to M. Hartman, June 2000).

The formulations registered for use on food and feed crops include the granular (G), wettable powder (WP), impregnated material (Impr), dry flowable (DF), and emulsifiable concentrate (EC). Dry flowable and wettable powder in open bags are not assessed and no longer are eligible for re-registration. These formulations may be applied as foliar, bark, seed, and soil-incorporated band or broadcast treatments using ground, sprinkler irrigation, or aerial equipment. The different crop growth stages or timings as to when chlorpyrifos formulations may be applied are dormant, delayed dormant, preplant, at-planting, transplanting, postplant, post-transplant, preemergence, and postemergence. The impregnated material formulation is registered for ear tag use on cattle. The chlorpyrifos formulations registered for food-handling establishments include the microencapsulated (Mcap), emulsifiable concentrate, and liquid ready-to-use (RTU) and soluble concentrate (SC/L) [Source: REFS 9/99].

4.2 Dietary Exposure

OPP has determined that TCP is not of toxicological concern and can be excluded from the tolerance expression because it does not inhibit cholinesterase (PP3F2884 and 3F2947 and FAP3H5396 and 3H5411/R1191, Final Rule, D.Barolo, 4/1/93). The conclusions specified in the "Tolerance Reassessment Summary" section of the Revised Product and Residue Chemistry Chapter (Memorandum from S. Knizner to M. Hartman, June 2000) reflect this decision and recommendation to consider only chlorpyrifos *per se* as the residue of concern. HED conducted a screening-level TCP assessment (memorandum from S. Knizner to D. Smegal, June 5, 2000, D265035).

4.2.1 Residue Chemistry Data Requirements

Plant and Animal Metabolism. The qualitative nature of the residue in plants and animals is adequately understood based on acceptable metabolism studies with a cereal grain (corn), a root and tuber vegetable (sugar beets), and acceptable poultry and ruminant metabolism studies. The residue of concern in plants and animals is chlorpyrifos *per se*. There are presently no direct application uses of chlorpyrifos on meat- and milk-producing animals, except for ear tag treatment of cattle (beef and lactating and non-lactating dairy).

Residue Analytical Methods - Plants and Animals. The requirements for residue analytical methods are fulfilled for purposes of re-registration. In consideration of HED's decision to regulate only the parent chlorpyrifos, acceptable methods are available for enforcement and data collection purposes. The behavior of chlorpyrifos using FDA's multi residue protocols has also been investigated and reported.

Storage Stability. The requirements for storage stability data are fulfilled for purposes of reregistration. Acceptable storage stability studies have been conducted on representative oil seeds, non-oily grains, root crops, fruits and fruiting vegetables, and low moisture content forage and hay. Additional studies have also been conducted to investigate the frozen stability of chlorpyrifos in selected processed food/feed commodities and in animal tissues and milk.

Magnitude of the Residue. The reregistration requirements for magnitude of the residue in plants (crop field trials and processed food/feed commodities) are fulfilled for the majority of crops. There are minor data gaps for asparagus, corn, cotton, crops grown solely for seed (clover and grasses), mint, peppers, sorghum, tomatoes, tree nut group and wheat. The reregistration requirements for magnitude of the residue in food-handling establishments are fulfilled. Sufficient data exist to determine that when registered formulations are used according to label directions, no detectable residues (<0.01-<0.025 ppm) are likely to occur in food items. Bait and insecticidal strip uses would not result in residues greater than those resulting from spray applications. Therefore, the outstanding data are considered confirmatory.

The reregistration requirements for magnitude of the residue in animals are fulfilled. There are presently no registered direct application uses of chlorpyrifos on livestock animals except for ear tag treatment of cattle (beef and lactating and non-lactating dairy). An acceptable residue transfer study of chlorpyrifos to milk and cream from dairy cows wearing chlorpyrifos-impregnated tags has been submitted; data from this study indicate that residues in whole milk and fat resulting from ear tag use should not be a significant fraction of the residues resulting from intake of animal feeds containing chlorpyrifos. Cattle and poultry feeding studies have been evaluated and found adequate to satisfy feeding study requirements.

Confined/Field Rotational Crops. Provided that the Registrant modifies all labels for its chlorpyrifos containing products to limit application to 5 lb ai/A/season on those crops where rotation to another crop could occur (as was stated in their letter to the Agency dated 8/12/94), HED will not require field rotational crop studies. Furthermore, a 30 day plant back interval for rotational crops would then be appropriate.

4.3 Dietary Exposure (Food Source)

As noted previously, chlorpyrifos is registered for use on a wide variety of food crops, and has approximately 112 tolerances for food and/or feed commodities (which translates to approximately 700 food forms in the dietary analysis). Food uses evaluated in this analysis were those reflected by the established tolerances in/on raw agricultural, animal, and processed food/feed commodities for chlorpyrifos as listed in 40 CFR §180.342. Food handling establishment (FHE) tolerances were also included as cited in 40 CFR §185.1000 for the chronic dietary analysis (i.e., as a result of the registered use in FHE, all foods have an established tolerance of 0.1 ppm, unless they are covered by higher tolerances). The tolerances published for chlorpyrifos under 40 CFR §180.342, 185.1000 and 186.1000 have been reassessed (HED Revised Product and Residue Chemistry Chapter, memorandum from S. Knizner to M. Hartman, June 2000). The established tolerances in/on raw agricultural, animal, and processed food/feed commodities are expressed either in terms of the combined residues of chlorpyrifos and its metabolite 3,5,6-trichloro-2-pyridinol (TCP) or as chlorpyrifos *per se.* HED has determined that TCP is not of toxicological concern and concluded that TCP can be excluded from the tolerance expression. Reassessed tolerances are in terms of chlorpyrifos *per se*. Thus, for purposes of this analysis, only residues of chlorpyrifos *per se* were considered, when data were available. Whenever possible, data for anticipated residues (ARs) reflect levels of chlorpyrifos *per se*. HED has conducted a screening-level risk assessment for TCP, which is in the attached memorandum from S. Knizner to D. Smegal, D265035 June 5, 2000.

Highly refined acute and chronic dietary exposure assessments were conducted using the Dietary Exposure and Evaluation Model (DEEM™) system. DEEM can be used to estimate exposure to residues in foods comprising the diets of the U.S. population, including population subgroups. The software contains food consumption data from the USDA Continuing Survey of Food Intake by Individuals (CFSII) from 1989-1992. For chronic dietary risk assessments, the 3-day average of the consumption data for each sub-population is combined with average residues in commodities to determine the average exposure in mg/kg/day. For acute dietary risk assessment, the entire distribution of single day food consumption events is combined with a distribution of residues (probabilistic analysis, referred to as "Monte Carlo") to obtain a distribution of exposures in mg/kg/day.

For chlorpyrifos, inputs to the DEEM analysis include DAS' National Food Survey (NFS, 1993 - 1994), U.S. Department of Agriculture's Pesticide Data Program (PDP) monitoring data (1994-1999), the Food and Drug Administration (FDA) Surveillance Monitoring Program data (1992-1998), and to a much lesser extent, field trial residue data. Percent crop treated data were supplied by the Biological and Economic Analysis Division (Quantitative Usage Analysis for Chlorpyrifos dated 3/30/00). Where percent crop treated estimates indicated no

chlorpyrifos use, a default minimum assumption of 1% crop treated was applied. In general, when residues on commodities were nondetectable, one-half the limit of detection (LOD) was assumed. All available processing and cooking factors were incorporated into the dietary exposure analysis.

At their own initiative, DAS conducted a market basket survey (NFS), with samples collected from the Fall of 1993 to the Fall of 1994, to better determine the dietary exposure of consumers to chlorpyrifos. The results of this survey have been reviewed by HED (L. Cheng, 5/19/98, D217707). Samples of fresh apple, applesauce, apple juice, orange juice, peanut butter, whole milk, ground beef and pork sausage were collected from grocery stores located in the 48 contiguous states; for fresh tomatoes, sampling was conducted in Florida only over a period of 9 months, because the domestic use of chlorpyrifos was restricted to Florida at the time of sampling. Approximately 200 samples were collected for each commodity, except for tomatoes, where 55 samples were collected. The nine food items were selected because of their significant contributions to dietary exposure in general (and in infants and children), and the potential for high residues based on modes of application and the percentage of crop treated. The apple and tomato samples were composite samples consisting of six apples and four tomatoes, respectively.

The Reference Dose (RfD) is derived from an exposure level at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, along with the application of uncertainty factors. The percent of the RfD is calculated as the ratio of the exposure value to the RfD (exposure/RfD x 100 = % RfD). The population adjusted dose (PAD) is the adjusted RfD reflecting the application of the FQPA safety factor. The FQPA safety factor for females and children is 10X, for all other populations subgroups it is 1X. For females and children, the population adjusted doses for acute and chronic dietary risk assessment are 0.0005 mg/kg/day and 0.00003 mg/kg/day, respectively. For all other population subgroups, the population adjusted doses for acute and chronic dietary risk assessment are 0.005 mg/kg/day and 0.0003 mg/kg/day, respectively. Exposures less than 100% of the PAD do not exceed HED's level of concern.

4.3.1 Acute Dietary Exposure Assessment

The HED probabilistic acute dietary exposure estimates used PDP, and FDA monitoring data to the greatest extent possible, in conjunction with the DAS's NFS data for all commodities included in the survey except apples and tomatoes. NFS data were used for milk, apple juice, applesauce, orange juice, ground beef, pork sausage, and peanut butter. A summary of the acute dietary analysis can be found in the attached memorandum from D. Soderberg to M. Hartman, June, 2000, D263890.

Three data sets are available for estimating residues on fresh apples: PDP data for analysis of individual single apples; PDP “decomposited”

apple data; and NFS "decomposited" apple data. Use of each of these three data sets for fresh apples leads to a different exposure estimate. The dietary exposure analysis has been performed using all commodities having chlorpyrifos uses and each of the apple data sets separately: PDP data for single apples; PDP "decomposited" apple data; and NFS "decomposited" apple data.

In 1999 PDP collected data on residues of chlorpyrifos on individual single apples. A total of 377 single apple samples were analyzed. Of these, 75 (20%) had measurable chlorpyrifos residues, ranging from 0.005 to 0.54 ppm. In an acute exposure analysis, results of analyses on single items of produce for a non-blended food are generally preferable to analyses of composite samples because they can be used without decompositing.

During 1994 - 1997, PDP also collected a total of 1908 composite apple samples, of which 425 samples (22%) had measurable chlorpyrifos residues, ranging from the ½ LOD for each laboratory (average 0.0026 ppm) to 0.4 ppm. Because fresh apples are considered to be a non-blended commodity, these results were decomposited using the Allender method (Allender, H. "Use of the Pesticide Data Program (PDP) in Acute Dietary Assessment", August 1998) to estimate single serving acute exposure.

DAS also submitted a market basket survey for fresh apples. All composite samples were collected from Fall 1993 - Fall 1994. There were 200 composite samples in this survey. A total of 68 samples (34%) had measurable chlorpyrifos residues, ranging from the LOD of 0.001 to 0.052 ppm.

Other programs have also analyzed fresh apples for chlorpyrifos. The FDA Surveillance Monitoring Program analyzed 1152 fresh apples (composites) between 1993 - 1998. FDA found 151 (13%) samples with measurable residues, ranging from 0.0005 ppm to 0.31 ppm.

FDA Total Diet Study (TDS) data are also available for chlorpyrifos, and in the case of apples these data also support use of the PDP data for risk assessment purposes. Measurable residues of chlorpyrifos (> 0.001 ppm) were found in apples for 14 of the 18 TDS surveys conducted from 1991 to 1997. Residues ranged from less than 0.001 ppm to 0.103 ppm, with a mean value of 0.012 ppm. Samples analyzed in the TDS are purchased at grocery stores and prepared according to standard consumer practices prior to analysis (in the case of apples this means washing). Samples are broadly composited in that composites are formed from samples purchased in three different cities from a given geographic region.

In summation, the maximum residue level found on composite apples in the NFS data is less than the maximum found in all other monitoring

programs, including the TDS, which most closely approximates NFS sampling.

NFS data on fresh tomatoes were submitted. However, only 54 samples were collected and all samples were from FL. More extensive and recent data for fresh tomatoes are available from PDP (881 samples, collected in 1996 and 1997). As was the case for apples, the highest reported detectable residue in the PDP data (0.31 ppm) was greater than that reported in the NFS data (0.0565 ppm). PDP monitoring data also reflect the use of chlorpyrifos on imported fresh tomatoes (a significant source of fresh tomatoes). Therefore the PDP fresh tomato residue data were used exclusively in all analyses. For commercially processed tomato commodities, PDP data were used but data obtained from FL grown tomatoes and fresh imported tomatoes were excluded, as these tomatoes are not used for processing. Appropriate processing residue reduction factors were incorporated for tomato juice, puree, catsup, and paste.

Exposure (consumption x residues) was compared to the acute population adjusted doses (aPAD) of 0.0005 mg/kg/day for children and females and 0.005 mg/kg/day for all other populations. The acute dietary risk analysis estimates the distribution of single day exposures for the overall U.S. population and certain subgroups. The analysis evaluates exposure to the chemical for each food commodity.

Table 3 summarizes the acute probabilistic dietary risk estimates for the U.S. Population and most highly exposed sub-populations. At the 99.9th percentile exposure, risk estimates based on the PDP single apple data, the decomposited PDP apple data, and/or the decomposited NFS apple data, were greater than 100% of the aPAD for the following population subgroups: all infants less than one-year old; children 1-6 years old; and children 7-12 years old. Children 1-6 years old were the most highly exposed population subgroup, regardless of which data set is used for fresh apples. For children 1-6 years old, risk estimates ranged from 170% to 355% of the aPAD depending on which fresh apple data set was used. Use of PDP's 1999 single apple data resulted in the highest exposure estimates. Use of the decomposited NFS fresh apple data resulted in the lowest exposure estimates.

Because the PDP single apple data are the most recent and do not require decompositing, these data are expected to provide the most reliable exposure and risk estimates. However, no matter which of the three data sets is used for fresh apples, the critical exposure commodity (CEC) analysis indicated that residues on fresh apples were the major contributor to dietary exposure estimates for children 1-6 years old at the 99.9th percentile exposure. Residues on whole tomatoes and grapes were the next major contributors to exposure.

Various risk reduction measures were examined to reduce acute dietary exposure and risk estimates. As was previously noted, fresh apples, fresh grapes and fresh tomatoes were the major contributors to acute dietary exposure for children 1-6 years old, the highest exposed subpopulation. Risk estimates could be reduced to less than 100% of the aPAD for children 1-6 years old only with mitigated exposure for all three of these commodities.

To mitigate exposure from fresh apples, the effect of deleting the late season foliar applications was examined. Currently, chlorpyrifos can be applied to apple trees when they are dormant or later in the season as a foliar treatment (up to 8 applications, with 21 days between the final two applications, and a 28 day PHI). In contrast to apples, chlorpyrifos can only be applied to pear trees as a dormant/delayed dormant application. PDP monitoring data are available for analysis of single pears. In the dietary exposure assessment, these data were translated to apples to determine the effect of deleting the apple foliar applications. Using this comparison,

residues on apples as a result of the dormant spray application are expected to be non-detectable (i.e., not expected to exceed 0.01 ppm). As part of risk mitigation, the tolerance for apples will be reassessed at 0.01 ppm, reflecting retention of only the pre-bloom application.

An examination of the PDP monitoring data for fresh grapes indicated that imported samples contained higher residues than domestic grapes. The current domestic use pattern limits application to a directed spray soil treatment to the base of dormant vines. Residues as a result of this application scenario are expected to be non-detectable (i.e., not exceed 0.01 ppm). The higher residues found on imported samples are most likely arising from later season foliar applications. As part of risk mitigation, the tolerance grapes will be reassessed at 0.01 ppm, reflecting the current domestic use pattern.

For tomatoes, PDP monitoring data again indicated that samples containing high residues were from imported fresh tomatoes. Chlorpyrifos is currently registered for use only in Florida (the state with the largest domestic production of fresh tomatoes) and Georgia. Information obtained from grower groups in FL indicates that chlorpyrifos is not used. Therefore, to mitigate dietary exposure the chlorpyrifos use on tomatoes will be deleted (i.e., tolerances revoked).

Based on these mitigation measures, risk estimates for all population subgroups are less than 100% of the aPAD as shown on Table 3. Children 1-6 years old remain the most highly exposed sub-population at 82% of the aPAD.

Table 3
Summary of Chlorpyrifos Acute Dietary Probabilistic Exposure and Risk Analysis (99.9th percentile)

Population Subgroup	PDP single apple monitoring data from 1999		"decomposited" PDP monitoring results for apples collected from 1994-1997		"decomposited" NFS monitoring results for apples collected from 1993-1994		Assuming Risk Mitigation (apples, tomatoes and grapes)	
	Exposure (mg/kg/day)	% aPAD (a)	Exposure (mg/kg/day)	% aPAD (a)	Exposure (mg/kg/day)	% aPAD (a)	Exposure (mg/kg/day)	% aPAD (a)
US Population	0.000790	16	0.000602	12	0.000453	9.1	0.000240	4.8
All Infants (< 1 year old)	0.000648	130	0.000548	110	0.000517	100	0.000258	52
Children 1-6 years old	0.001779	355	0.001247	250	0.000855	170	0.000410	82
Children 7-12 years old	0.001288	258	0.000939	190	0.000607	120	0.000319	64
Females 13-50 years old	0.000635	127	0.000484	97	0.000375	75	0.000201	40
Males 20+ years old	0.000580	12	0.000456	9.1	0.000359	7.2	0.000205	4.1

(a) The acute population adjusted dose (aPAD) is 0.0005 mg/kg/day for females and children and 0.005 mg/kg/day for all other sub-populations. Values rounded to two significant figures.

The uncertainties in the acute dietary exposure estimates are discussed below following the chronic dietary exposure assessment discussion.

4.3.2 Chronic Dietary Exposure Assessment

A refined chronic exposure analysis was performed using the DEEM ™ exposure modeling software. The input values included the PDP, FDA and DAS' NFS data, in addition to average residues from field trials and percent of the crop treated information from BEAD. All NFS data available were used except for fresh apples and tomatoes, for which PDP monitoring data were used. An additional analysis was conducted using NFS data for apples. Exposure (consumption) was compared to the chronic population adjusted dose (cPAD) of 0.00003 mg/kg/day for females and 0.0003 mg/kg/day for all other subpopulations. A summary of the residue information included in this analysis can be found in the attached memorandum from D. Soderberg to M. Hartman, June, D263889.

As shown in Table 4, for both risk estimates based on PDP or NFS data for fresh apples, the average chronic dietary residue contributions with or without the food handling establishment use are less than 100% of the cPAD and thus do not exceed HED's level of concern. Based on PDP monitoring data for fresh apples, without consideration of the food handling establishment use, the average exposure estimates comprised 3% and 61% of the cPAD for the general population and the most highly exposed subgroup, children 1-6 years old, respectively. The average exposure estimates including the food handling establishment use comprised 4% and 81% of the cPAD for the general population and for the most highly exposed subgroup, children 1-6 years old, respectively.

For the dietary exposure analysis using NFS fresh apple data, dietary risk estimates ranged from 3% to 57% for the general population and children 1-6 years of age, respectively without the food handling establishment tolerance. With food handling establishment tolerances, the dietary risk estimates ranged from 3% to 63% for the general population and children 1-6 years of age, respectively.

The effect of the risk mitigation measures discussed above, on the chronic dietary risk estimates was examined. Based on the mitigation measures (i.e., reduction of apple tolerance to 0.01 ppm based on pre-bloom application, reduction of grape tolerance to 0.01 based on domestic use pattern, and deletion of the use on tomatoes), chronic dietary risk estimates were also reduced, as shown on Table 4. Children 1-6 years old remain the most highly exposed subpopulation, with risk estimates of 51% and 36% of the cPAD, including the FHE use or using zero residues for the FHE use, respectively.

Table 4
Summary of Chlorpyrifos Chronic Dietary Exposure Analysis(a)

Population Subgroup	Estimate w/PDP Apple Data				Estimate w/NFS Apple Data				Assuming Risk Mitigation (apples, tomatoes and grapes)			
	Excludes Food Handling Establishment Use		Includes Food Handling Establishment Use		Excludes Food Handling Establishment Use		Includes Food Handling Establishment Use		Excludes Food Handling Establishment Use		Includes Food Handling Establishment Use	
	Average exposure (Fg/kg BW/day)	% cPAD	Average Exposure (Fg/kg BW/day)	% cPAD	Average exposure (Fg/kg BW/day)	% cPAD	Average Exposure (Fg/kg BW/day)	% cPAD	Average exposure (Fg/kg BW/day)	% cPAD	Average Exposure (mg/kg BW/day)	% cPAD
US Population	0.008	3	0.012	4	0.008	3	0.008	3	0.004	1.4	0.008	2.5
All infants (< 1 yr)	0.007	23	0.014	45	0.007	24	0.008	28	0.003	11	0.01	33
Children (1-6 years)	0.018	61	0.024	81	0.017	57	0.019	63	0.009	31	0.015	51
Children (7-12 years)	0.013	45	0.018	59	0.012	41	0.014	46	0.006	21	0.011	36
Females 13-50 years	0.006	21	0.009	30	0.006	20	0.006	22	0.003	11	0.006	20

(a) Values based on DEEM output, and are based on non-rounded exposure results.

Uncertainties of Dietary Exposure Estimates

The Agency believes the risk assessment presented is the most refined to date for acute and chronic dietary exposure to chlorpyrifos. However, there are some uncertainties associated with these exposure estimates as follows:

(a) Residues were detected in PDP over several years for a number of commodities that lack chlorpyrifos tolerances (i.e., chlorpyrifos is not registered for use on these commodities). These include spinach, squash, and carrots as shown below in Table 5:

Table 5
Commodities with Detected Residues in PDP and Frequently Fed to Children that Lack Established Chlorpyrifos Tolerances

Commodity	Year	# Samples with Detections	% Samples with detections	Minimum Residue Detected (ppm)	Maximum Residue Detected (ppm)
Carrots	1994	2	0.3	0.005	0.005
	1995	6	0.9	0.005	0.019
	1996	7	1.4	0.005	0.074
Spinach	1995	46	7.5	0.005	0.11
	1996	26	5.0	0.003	0.030
	1997	11	2.1	0.005	0.026
	1998 (canned)	4	0.6	0.007	0.014
Squash	1997	4	1.8	0.005	0.005
	1998	6	1.1	0.005	0.022

Residues were also detected in celery (4 samples in 1994, 0.005 - 0.045 ppm), potatoes (1 sample in 1994, 0.024 ppm), and lettuce (1 sample in 1994 at 0.01 ppm).

The FDA Total Diet Study also contains data indicating that chlorpyrifos residues in/on spinach may occur. Measurable chlorpyrifos residues have been found on cooked spinach in 10 of 18 market basket surveys (56%) conducted from 1991 to 1997.

These residue results were not included in the Agency's dietary exposure assessment as they represent misuse of chlorpyrifos. However, because these violations have occurred over the years,

excluding them might have under-represented potential dietary exposure, especially for infants and children. Therefore, an additional set of dietary exposure assessments have been performed including results for squash, spinach and carrots - three commodities frequently fed to infants and children. Celery, lettuce and potatoes were not included. These additional assessments were not significantly different from the mitigated acute or chronic dietary assessments.

(b) The consumption database used in the dietary exposure analysis (CSFII, 1989-1992) has a limited number of individuals in the age group infants less than one year old (approximately 100). The USDA is currently conducting the Supplemental Children's Survey (approximately 5000 children).

(c) The dietary exposure analyses relied primarily on monitoring data obtained either "at the farmgate" in the case of FDA or in regional distribution warehouses for PDP data. The NFS results are for samples obtained at supermarkets, but only represent one year of data. Residues potentially present on items purchased at roadside produce stands or farmer's markets are not represented in this analyses.

(d) The acute dietary analysis does not include FHE use, in accordance with current policy.

(e) Potential exposure to chlorpyrifos residues from consumption of fish was not addressed. No tolerances for fish are currently established. In 1992 the Agency's Office of Water (OW) published a report (EPA 1992) that summarized chlorpyrifos residues found in freshwater fish in lakes and rivers at that time. The primary focus of the study was monitoring for dioxin/furan in fish. However, chlorpyrifos residues were detected in 26% of the 388 sites tested, with median, mean, and maximum concentrations of non-detect, 4.09, and 344 ppb respectively. This study indicated that consumption of freshwater fish (i.e., sport fisherman and their families, or others) could contribute to dietary exposure to chlorpyrifos. FDA also has monitored farm-raised fish for chlorpyrifos. Of all fish and crustacean samples tested between 1992 to 1998, FDA found residues of chlorpyrifos in one trout (1994) and twelve catfish (four catfish in each year 1992 - 1994). FDA has found no detectable residues of chlorpyrifos in any farm-raised fish from 1995 to 1998. This is discussed in more detail below.

Chlorpyrifos Screening-Level Exposures and Risks from Freshwater Fish Consumption

In 1992, the EPA Office of Water (OW) published a report that summarized the chlorpyrifos residues in freshwater fish, and evaluated the health risks to individuals that consume freshwater fish as part of a National Screening Assessment (EPA 1992). The results of the EPA OW Assessment were not included in HED's dietary analysis because of the screening-level nature of this investigation (i.e., limited fish samples collected in areas of chlorpyrifos use, and a greater focus on bottom feeding fish such as carp and white sucker that do not contribute significantly to the diet). Nevertheless, this study indicates that consumption of freshwater fish could also contribute to the dietary exposures and risks of chlorpyrifos for sports fisherman and their families. The results of this assessment are presented below.

In the OW study, game and bottom feeding fish were collected from 388 sites, of which 314 were near point and non point sources of pollution, 39 locations were from the U.S. Geological Survey (USGS) National Stream Quality Accounting Network (NASQAN), and 35 locations represented background levels. The selection of sites was biased toward sites where dioxin/furan concentrations in fish are expected (i.e., near pulp and paper mills and industrial sources), because the original intent of study was to investigate these compounds. Consequently, few of the sites (n=15) investigated were near agricultural areas, where chlorpyrifos use is pervasive.

Chlorpyrifos was detected in fish from 26 percent of the 388 sites, with median, mean and maximum concentrations of non detect, 4.09 and 344 Fg/kg (ppb), respectively. (The second highest concentration was 64.5 Fg/kg). Over 70 percent of the fish concentrations at all sites were below detection. The highest concentrations were observed primarily in bottom feeding fish such as carp near agricultural facilities. The mean concentration from agricultural areas was 24.46 Fg/kg. In general, chlorpyrifos concentrations were detected in whole-body samples of bottom feeders and in fillet samples of game fish at roughly the same average concentration.

Health risks were calculated using fillet samples of game fish collected from 106 sites. Risk estimates were calculated using standard EPA risk assessment procedures, an average fish consumption rate of 6.5 g/day for the U.S. population, daily fish consumption over a lifetime of 70 years, and the chlorpyrifos RfD on EPA's Integrated Risk Information System (IRIS) of $3x10^{-3}$ mg/kg/day (which is an order of magnitude higher than the RfD developed by HED). The resulting hazard indices associated with ingestion of the maximum and mean chlorpyrifos fillet concentrations were

$2.4x10^{-3}$ and $6.4x10^{-5}$, respectively for the U.S. population. These risk estimates are both < 1% of the EPA RfD on IRIS, and would represent 24% and < 1% of the HED chronic PAD, respectively for chronic consumption of the maximum and mean fillet concentrations. However, it is unlikely that an individual would chronically consume the maximum detected residue of 344 Fg/kg, therefore, it may be more appropriate to compare this dose estimate to the acute PAD than the chronic PAD. In this case, consumption of fish containing 344 Fg/kg reflects only 1.4% of the aPAD.

The potential chlorpyrifos exposures could be higher for Native Americans or other subsistence populations that typically consume more freshwater fish than the general U.S. population. USEPA (1997) reports average and 95th percentile fish consumption rates of 70 g/day and 170 g/day, respectively for Native American Subsistence Populations. Consequently, potential exposures and risks could be 11 to 26 times higher than those reported for the general population of sport fisherman and their families. Risk estimates could potentially exceed HED's level of concern if chlorpyrifos fish fillet residues of 344 Fg/kg were ingested daily for 70 years at rates of 70 to 170 g/day. However, subsistence populations are not expected to have exposures or risks that exceed HED's level of concern following chronic ingestion of fish fillets with mean chlorpyrifos concentrations of 4.08 Fg/kg (up to 26% of the aPAD).

4.3.3 Drinking Water Exposure

The Environmental Fate and Effects Division (EFED) conducted a drinking water assessment for chlorpyrifos based on an analysis of existing ground and surface water monitoring data in conjunction with conservative Tier 1 and Tier 2 modeling (using GENEEC 1.2, PRZM 2.3-EXAMS, and SCI-GROW) (Attached memo from H. Nelson to D. Smegal/M. Hartman, October 6, 1999 and M. Barrett to S. Knizner, November 13, 1998). The drinking water exposure estimates are discussed in greater detail below by water source.

The available environmental fate data suggest that chlorpyrifos has a low potential to leach to groundwater from most typical agricultural uses in measurable quantities, except following termiticide use. Chlorpyrifos is persistent in concentrated applications used in termiticide treatments. The available data indicate that the primary metabolite of chlorpyrifos, 3,5,6-TCP is more mobile, and significantly more persistent in many soils, especially under anaerobic conditions.

Currently, HED uses Drinking Water Levels of Comparison (DWLOCs) as a surrogate to capture risk associated with exposure to pesticides in drinking water. A DWLOC is the concentration of a pesticide in drinking water that would be acceptable as a theoretical upper limit in light

of the total aggregate exposure to that pesticide from food, water, and residential uses. HED uses DWLOCs in the risk assessment process as a surrogate measure of potential exposure associated with pesticide exposure through drinking water. In the absence of reliable monitoring data for a pesticide, the DWLOC is used as a point of comparison against the conservative estimated environmental concentrations (EECs) provided by computer modeling (SCI-GROW, GENEEC, PRZM/EXAMS). A DWLOC may vary with drinking water consumption patterns and body weights for specific subpopulations.

HED back-calculates DWLOCs by a two-step process: exposure [food + (if applicable) residential exposure] is subtracted from the PAD to obtain the maximum exposure allowed in drinking water; DWLOCs are then calculated using that value and HED default body weight and drinking water consumption figures. In assessing human health risk, DWLOCs are compared to EECs. When EECs are **greater** than DWLOCs, HED considers the aggregate risk [from food + water + (if applicable) residential exposures] to exceed HED's level of concern.

4.3.3.1 Groundwater Exposure Levels

EFED conducted an analysis of over 3000 filtered groundwater monitoring well data available in U.S. Geological Survey's National Water Quality Assessment (NAWQA) Program databases, and in EFED's Pesticides in Ground Water Data Base (PGWDB). Chlorpyrifos was infrequently detected in groundwater (< 1% of the 3000 wells). The majority of concentrations were reported to be <0.01 Fg/L, with only occasional contamination at a maximum level of 0.026 Fg/L. Although the available monitoring data represent a large part of the U.S., it is not clear that they represent the most vulnerable groundwater where chlorpyrifos is used most intensively. The Pesticides in Ground Water Database (PGWDB) reports a maximum detected concentration of 0.65 Fg/L.

EFED also performed screening-level model estimates of chlorpyrifos concentrations in groundwater using SCI-GROW for four crops (corn, cotton, alfalfa and citrus). The estimated chlorpyrifos concentrations in groundwater using the SCI-GROW screening model range from 0.007 Fg/L (typical application to alfalfa) to 0.103 Fg/L (maximum multiple applications to sweet corn). Therefore, based on an analysis of both monitoring and modeling data, EFED concludes the large majority of the country (>99%) will not have potable groundwater that contains chlorpyrifos at levels greater than 0.1 Fg/L. EFED recommends a range of 0.007 to 0.103 Fg/L as conservative EECs to be used to evaluate both acute and chronic exposures. The

NAWQA monitoring data support that the SCI-GROW modeling estimates are conservative.

Chlorpyrifos use as a termiticide is significant, with a recent estimate of seven million pounds ai applied annually constituting about 30% of the total annual use. Chlorpyrifos groundwater exposure from termiticidal use is highly localized and usually only in wells located within 100 feet of the treatment area. For this use, the maximum detected dissolved concentration is 2090 Fg/L with unknown chronic exposure levels that are presumably significantly lower, but that can persist at detectable levels for at least 6 months. EFED recommends an upper bound range of 30 to 2090 Fg/L to evaluate acute groundwater exposures following termiticide use. The 30 Fg/L represents the concentration that DAS recommends before resuming the use of a contaminated well (i.e., current USEPA Health Advisory for a child), while the 2090 Fg/L concentration represents the maximum detected value. EFED recommends a range of 8.3 to 578 Fg/L to be used to evaluate upper bound chronic groundwater exposures for termiticide use. These values are the acute groundwater termiticide concentrations with adjustments for partial environmental degradation (abiotic hydrolysis at pH 7). DAS states that this exposure only occurs in homes where the well casing has a crack in it, and the well is near or in the foundation. HED has determined that the Label Improvement Process for Termiticides (PR notices 96-7 for termiticides) have reduced the potential for this exposure. For example, reported incidents associated with termiticide use were 28.2 per 100,000 homes in 1997 (pre PR-96-7), and were 8.3 per 100,000 homes in 1998 (post PR-96-7).

4.3.3.2 Surface Water Exposure Levels

EFED conducted an analysis of over 3000 samples from 20 NAWQA study units for flowing surface water collected from rivers and streams over the last several years. Chlorpyrifos was detected at frequencies up to 15% of 1530 agricultural streams, 26% of 604 urban stream samples in 1997 and in 65% of 57 urban stream samples from Georgia, Alabama and Florida in 1994. The maximum reported dissolved chlorpyrifos concentration in surface water was 0.4 Fg/L, with the majority of detected concentrations < 0.1 Fg/L. EFED notes that although the available monitoring data represent a large part of the U.S., the monitoring data may not represent the most vulnerable watersheds where chlorpyrifos use is pervasive. EFED notes that a limited number of watersheds in the U.S. may have chlorpyrifos concentrations higher than 0.4 Fg/L due to higher usage rates or greater pesticide runoff. In particular, acute exposure levels could be higher for streams draining watersheds with more intense chlorpyrifos use or for lakes and reservoirs for which there are little data.

EFED also performed screening-level model estimates of chlorpyrifos concentrations in surface water such as lakes and reservoirs using Tier I GENEEC or Tier II PRZM/EXAMS. Inputs to the models included high exposure agricultural scenarios for major crops (alfalfa, corn, citrus, and tobacco) at the maximum application rates. Estimated maximum 90 day average and peak concentrations of chlorpyrifos in surface water using the PRZM/EXAMS screening model were 6.7 Fg/L and 40.6 Fg/L, respectively. These estimated concentrations should be highly conservative for most surface waters and all drinking water because they are based on a pond draining an adjacent 100% treated field model (it is highly unlikely that 100% of a watershed constituting a major drinking water source would be treated with chlorpyrifos in a given year).

Based on an analysis of the NAWQA monitoring and EFED modeling data, an upper-bound EEC range of 0.026 to 0.4 Fg/L was selected to assess acute risks associated with non-termiticide uses of surface water. The 0.026 Fg/L concentration represents the 95th percentile dissolved concentration, while the 0.4 Fg/L concentration is the maximum detected dissolved chlorpyrifos concentration from streams and rivers reported in the first phase of the NAWQA study. The 95th percentile concentration of 0.026 Fg/L was used to assess chronic surface water exposures. The Agency concluded that the 0.4 Fg/L estimate (a high acute exposure level for streams) is more reasonable than the conservative PRZM/EXAMS maximum peak EEC of 40.6 Fg/L for lakes and reservoirs. This is because multi-month or annual mean concentrations in a reservoir are expected to be less than the maximum reported concentrations in the flowing water feeding the reservoir. The monitoring data also demonstrate that chronic concentrations of chlorpyrifos are unlikely to exceed 0.1 Fg/L. These estimates only apply to drinking water because residues of lipophilic pesticides, such as chlorpyrifos, bound to sediment and suspended solids could contribute to exposure following consumption of unfiltered water.

4.3.3.3 Drinking Water Exposure Concentrations

The estimated environmental concentrations (EECs) are shown on Table 6. As noted previously, the groundwater EECs are based on conservative modeling, with support from monitoring data, while the surface water EECs are based on upper-bound levels from monitoring data.

Table 6 ESTIMATED ENVIRONMENTAL CONCENTRATION (EECs)		
Drinking Water Source	Concentration (Fg/L)	
	Acute	Chronic
Groundwater, except for well contamination SCI-GROW (Fg/L) (a)	0.007 to 0.103	
Groundwater as a result of well contamination (Fg/L)	30 to 2090	8.3 to 578
Surface Water Monitoring Data (Fg/L)	0.026 to 0.4 (b)	0.026 (c)

(a) SCI-GROW (Screening Concentration in Ground Water) is an empirical model for predicting pesticide levels in ground water. The value from SCI-GROW is considered an upper bound concentration estimate.
(b) Based on the 95th percentile and maximum detected surface water concentrations.
(c) Based on the 95th percentile surface water concentration from monitoring data

In comparison, the one-day, 10-day, and longer-term USEPA health advisories for a 10-kg child are 30 Fg/L. The lifetime health advisory for a 70-kg adult has been established at 20 Fg/L; the adult longer-term health advisory is 100 Fg/L.

EFED notes that there are significant uncertainties associated with the EECs which are as follows:

(1) The estimates are intended to be as realistic as possible but apply only to the most vulnerable populations because existing monitoring data imply that the majority of the U.S. population will not be exposed at these levels (for surface water note that the 95th percentile estimate is 15 times less than the maximum detected value in monitoring data);

(2) All of these estimates are for unfinished water, and could be lower in finished drinking water that has received treatment; and

(3) The exposure estimates are highly conservative (i.e., exceed actual exposure by several-fold) for the majority of the U.S. population, based on the existing monitoring database, which covers a large part of the U.S. However, chlorpyrifos residues in surface waters could be higher in some areas where chlorpyrifos usage is more pervasive in the watershed.

4.3.3.4 DWLOCs for Acute (Drinking Water) Exposure

Acute DWLOCs were not calculated for chlorpyrifos initially because the acute dietary risks alone exceed HED's level of concern based on currently registered uses. Therefore, in effect, the DWLOCs would be zero. However, acute DWLOCs were calculated based on risk mitigation measures that reduce the acute dietary risk estimates to below 100% of the aPAD.

The acute DWLOC values are presented in Table 7. For each population subgroup listed, the acute PAD and the acute dietary (food) exposure (from Table 3) for that subgroup were used to calculate the acute DWLOC for the subgroup, using the formulas in footnotes of Table 7. The EECs are less than the DWLOCs for all populations (highest EEC of 0.4 Fg/L is less than the lowest DWLOC of 0.9 Fg/L), indicating that acute food and drinking water exposures (except possible well contamination) do not exceed HED's level of concern. It should be noted that neither the SCI-GROW model nor the monitoring data reflect concentrations after dilution (from source to treatment to tap) or drinking water treatment.

Table 7
DWLOCs for Chlorpyrifos Acute Dietary Exposure Considering Mitigation Measures

Population Subgroup (a)	Acute PAD (Fg/kg/day)	Food Exposure 99.9th (Fg/kg/day) (b)	Max. Water Exposure (Fg/kg/day) (c)	Surface Water (Monitoring Data) (Fg/L)	Ground Water SCI-GROW, (excluding well contamination) (Fg/L)	Acute DWLOC (Fg/L) (d,e,f)
U.S. Population	5	0.24	4.76	0.026 to 0.4	0.007 to 0.103	166
All Infants (< 1 Year)	0.5	0.258	0.242			2.4
Children (1-6 years)	0.5	0.410	0.09			0.9
Females (13-50 years)	0.5	0.201	0.299			9

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.
(b) 99.9th percentile exposure. Values are from Table 3 (and rounded).
(c) Maximum Water Exposure (Fg/kg/day) = Acute PAD (Fg/kg/day) - [Acute Food Exposure (Fg/kg/day)].
(d) DWLOC (Fg/L) = Maximum water exposure (Fg/kg/day) x body wt (kg) ÷ water consumed daily (L/day)]
(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

Acute exposure to chlorpyrifos in groundwater as a result of well contamination from termiticide use could potentially result in exposures of concern. However, as noted previously, the groundwater exposures from well contamination resulting from termiticide use are highly localized. The implementation of PR 96-7 for termiticides has reduced reported incidents of groundwater contamination resulting from termiticide treatments. For example, reported incidents associated with termiticide use were 28.2 per 100,000 homes in 1997 (pre PR-96-7), and were 8.3 per 100,000 homes in 1998 (post PR-96-7).

4.3.3.5 DWLOCs for Chronic Drinking Water Exposure

The chronic DWLOC is effectively zero because the long-term residential postapplication risks alone exceed HED's level of concern. However, DWLOCs were calculated based on food (including food handling establishment uses) and water exposure alone. The chronic DWLOC values are presented in Table 8. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 4) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes of Table 8. As shown, the EEC for surface water (which represents the 95th percentile concentration from monitoring data) is less than the DWLOCs, and therefore does not exceed HED's level of concern. It should be noted that neither the SCIGROW model nor the monitoring data reflect actual drinking water concentrations after dilution (from source to tap) or drinking water treatment.

Table 8
DWLOCs for Chlorpyrifos Chronic Dietary Exposure
Includes Mitigation

Population Subgroup (a)	Chronic PAD (Fg/kg/day)	Chronic Food Exposure with FHE (Fg/kg/day) (b)	Max. Water Exposure (Fg/kg/day) (c)	Surface Water Monitoring Data (Fg/L)	Ground Water SCI-GROW (excluding well contamination) (Fg/L)	Chronic DWLOC (Fg/L) (d,e,f)
U.S. Population	0.3	0.008	0.292	0.026	0.007 to 0.103	10
All Infants (< 1 Year)	0.03	0.01	0.02			0.2
Children (1-6 years)	0.03	0.015	0.015			0.15
Females (13-50 years)	0.03	0.006	0.024			0.72

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.
(b) Values are from Table 4 (and rounded).
(c) Maximum Water Exposure (Fg/kg/day) = Chronic PAD (Fg/kg/day) - [Chronic Food Exposure + Chronic Residential Exposure (Fg/kg/day) (if applicable)]. Chronic residential uses were not considered based on mitigation options.
(d) DWLOC (Fg/L) = Maximum water exposure (Fg/kg/day) x body wt (kg) ÷ water consumed daily(L/day)]
(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

Long-term exposure to chlorpyrifos as a result of well contamination from termiticide use could potentially result in exposures of concern. However, as noted previously, the groundwater risk estimates from well contamination resulting from termiticide use are highly localized. The implementation of PR 96-7 for termiticides has reduced the reported incidents of groundwater contamination resulting from termiticide treatments.

4.4 Non-Dietary Exposure

Chlorpyrifos is an organophosphate insecticide used extensively in residential settings by both residents and PCOs, and for agricultural use (e.g., citrus, vegetable crops, tree fruits, etc.), greenhouse uses, outdoor ornamental uses, and sodfarm uses. It is one of the top five insecticides used in residential settings. There are approximately 800 registered products containing chlorpyrifos on the market (REFs 9/14/99). Registered uses include a wide variety of food, turf and ornamental plants, as well as indoor products, structural pest control, and in pet collars. It is used in residential and commercial buildings, schools, daycare

centers, hotels, restaurants, hospitals, stores, warehouses, food manufacturing plants and vehicles. In addition, it is used as an adult mosquitocide. In 1998, the DAS estimated that 70% of the urban chlorpyrifos use involved termite control. Approximately 11 million pounds a.i. are applied annually in non-agricultural settings (i.e., residences, schools, golf courses, parks).

Chlorpyrifos, is formulated as a wettable powder packaged in water soluble packets (containing 50% a.i.), emulsifiable concentrates (41.5-47%), dust (containing 0.1-7% a.i.), granular (containing 0.075%-15% a.i.), bait (containing 0.5% a.i.), flowables (containing 30% a.i.), impregnated material (containing 0.5-10% a.i.), pelleted/tableted (containing 0.5-1.0% a.i.), pressurized liquids (0.9-3.8% a.i.), microencapsulated (0.5-20% a.i.) and soluble concentrate/liquids (0.5 to 62.5% ai). Dry flowables and wettable powder in open bags are not supported by the registrant, and therefore, the assessment of these formulation types/packaging is not included in this document. According to DAS, formulations with concentrations greater than one pound a.i. per gallon (approximately 13% a.i.) are sold to licenced pest control or turf and ornamental professionals only. Lower concentrations are available to homeowners from other suppliers for over-the-counter purchase. Except aerosols, granules and dusts, all formulations for application are diluted in water to a concentration of 1 percent a.i. or less (Dow AgroSciences 1998). However, HED is aware of at least one company that sells concentrated chlorpyrifos products (i.e., >13% up to 44.8% ai) to the public on the Internet (www.ADDR.com/~pestdepo/gizhome.htm) as of March 1, 2000.

Occupational and residential exposures to chlorpyrifos can occur during handling, mixing, loading and applying activities. Occupational postapplication exposure can occur for agricultural workers during scouting, irrigation and harvesting activities. Residential postapplication exposure can occur following treatment of lawns, or residences for cockroaches, carpenter ants, termites, and other insects. In addition, there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated turf and soil or hand to mouth activities following contact with treated surfaces or turf. Postapplication exposure to children can occur in locations other than the home, including schools, daycare centers, playgrounds, and parks. There is insufficient use information and exposure data to assess exposure resulting from use in vehicles (i.e., planes, trains, automobiles, buses, boats) and other current label uses such as treatment of indoor exposed wood surfaces, supermarkets, theaters, furniture, and draperies. However, HED has concern for these uses based on the scenarios assessed within this document, and has requested exposure data for all uses of registered products not currently assessed in this document. Although there is concern for these uses, the Agency believes that exposure from these uses will not be higher than the scenarios evaluated in this assessment.

Based on toxicological criteria and potential for exposure, HED has conducted dermal and inhalation exposure assessments for the occupational and residential handlers, occupational postapplication, in addition to residential postapplication dermal, inhalation to adults and children and inadvertent oral exposure to children.

Details of the agricultural and ornamental exposure scenarios are presented in the attached memorandum from T. Leighton to D. Smegal/M. Hartman, D263893, June 2000. Details of the occupational/residential handler assessment for residential settings and the postapplication residential risk assessment are presented in the attached memorandum from D. Smegal/T. Leighton to M. Hartman, D266562, June 2000.

4.4.1 Occupational Handler Exposure Scenarios

HED has identified 26 major exposure scenarios (resulting in 56 assessments) for which there is potential occupational handler exposure during mixing, loading, and applying products containing chlorpyrifos to agricultural crops and ornamentals (16 scenarios) and to non-agricultural use sites (10 scenarios) such as residential or recreational settings. These occupational scenarios reflect a broad range of application equipment, application methods and use sites. For agricultural uses, application techniques include tractor-drawn equipment, open and closed mixing/loading, and hand held equipment. The application rates used in the assessment are intended to reflect the upper range of rates on the labels. Maximum rates are always included in the assessment to provide a hazard evaluation for those individuals that may use the label as approved by the Agency. In some instances, the rates also include values Dow AgroSciences (DAS) specifically requested to be included as "typical" (e.g., a variety of sod farm rates, corn, citrus, greenhouse, and various nursery rates).

DAS has recently submitted a market survey (Mar-Quest) and the Agency is currently reviewing the results before including additional characterization of chlorpyrifos typical use conditions. HED also included the typical, or median use rates of 1 and 2 lb ai/acre for treatment of surface and subsurface-feeding insects on turf, respectively based on lawn care data submitted by the Registrant and TruGreen/ChemLawn (Jefferson Davis Associates, 1999, TruGreen/ChemLawn 1999). Examples of the application rates used in this assessment include, but are not limited to the following: liquid turf treatment from 1 to 4 lb ai/acre, granular turf treatment at 2 lb ai/acre, vegetable crops range from 1 to 2 lb ai/acre; maximum citrus rate is 6 lb ai/acre; the maximum rates for tree nuts and fruits is 2 lb ai/acre; outdoor ornamental rates for wettable powders are up to 4 lb ai/acre and up to 0.16 lb ai/gallon for liquid formulations; and up to 8 lb ai/acre for fire ant control in sodfarm turf just prior to harvest. The predominant maximum application

rates are defined as those rates which are most frequently cited in the labels and are also believed to be representative of the maximum allowable rates that would not underestimate exposure. Even though an attempt was made to include rates requested by DAS, some of the rates assessed do not necessarily reflect all of the typical rates used on those crops such as the tobacco rate (i.e., only maximum rate of 5 lb ai/A assessed).

The scenarios were classified as short-term (1 to 30 days), intermediate-term (1 to 6 months) and in some cases long-term (greater than 6 months) based primarily on frequency of exposure. The occupational handler scenarios for agricultural use are expected to be of a short-term duration only. It is believed that if there are any agricultural applicators applying chlorpyrifos daily for over a month, those individuals will represent a very small segment of the population. Moreover, those individuals would not be applying the amount of chemical estimated to be handled at the maximum rates in the short-term assessment. On the other hand, several of the LCO/PCO handler scenarios in residential settings (i.e., treatment of homes for insect infestations) were considered to be long-term duration. For the agricultural handlers, the estimated exposures considered personal protective equipment (PPE, which includes a double layer of clothing and gloves and/or a dust/mist respirator), and engineering controls (closed mixing/loading systems for liquids and granulars and enclosed cabs/trucks). Baseline attire (long pants, long sleeved shirt, no gloves) is not presented in this assessment to conserve resources and because of the need for additional PPE and/or engineering controls for all scenarios, and the labels currently require PPE. For LCO/PCO exposure scenarios in residential settings, in most cases only exposures associated with the label-recommended clothing were considered (i.e., scenarios with additional PPE or engineering controls could not be evaluated) based on chemical-specific studies submitted by DAS (many of which include biological monitoring).

4.4.1.1 Occupational Handler Exposure Data Sources and Assumptions

Multiple chemical-specific handler exposure studies were conducted by the registrant and submitted to the Agency. The handler data collected included biological monitoring of urinary 3,5,6-TCP, the primary metabolite of chlorpyrifos, and passive dosimetry data. These chemical-specific exposure data are used by the Agency to assess the potential handler exposures to chlorpyrifos. However, of the five agricultural monitoring studies submitted by DAS, only two of the studies measured at least 15 replicates (minimum as per the Pesticide Assessment Guideline criteria) of a specific activity (one measuring 15 replicates of both mixer/loader and airblast applicators, the other study measuring 16 replicates of a

combined mixer/loader/applicator for a granular formulation). As for the other three studies, one study measured 13 replicates of an applicator applying chlorpyrifos with various types of high pressure handwands in a greenhouse, 1 replicate of a low pressure handwand, and 2 replicates of a backpack sprayer; the second study measured 9 replicates of an open cab groundboom applicator, 6 replicates of an open mixing/loading EC formulation, and 3 replicates of an open bag WP formulation (open bag WP formulation no longer supported by DAS); and the final study measured 14 replicates of an open mixing/loading of liquids for aerial applicators. Therefore, three of the five DAS studies contain an insufficient number of replicates (as specified by Subdivision U Guidelines) to support the exposure scenarios. Moreover, the total of five agricultural studies submitted by DAS in support of the chlorpyrifos reregistration do not encompass all of the uses of the chemical on the labels nor do they all provide sufficient mitigation (e.g., PPE or engineering controls) to meet an occupational target MOE of 100.

In the absence of applicable chemical-specific data, agricultural handler and LCO/PCO potential exposures resulting from handling and applying chlorpyrifos were estimated using data from the Pesticide Handlers Exposure Database (PHED) Version 1.1 or the Draft Residential SOPs. PHED was designed by a Task Force of representatives from the U.S. EPA, Health Canada, the California Department of Pesticide Regulation, and member companies of the American Crop Protection Association. PHED is a software system consisting of two parts -- a database of measured exposure values for workers involved in the handling of pesticides under actual field conditions and a set of computer algorithms used to subset and statistically summarize the selected data. Currently, the database contains values for over 1,700 monitored individuals (i.e., replicates). HED's policy is to supplement chemical-specific data with available surrogate data in PHED to increase the sample size (U.S. EPA and HC 1995a - PHED V1.1 Evaluation Guidance). This policy is in effect because individual chemical-specific studies, even when fulfilling the Guideline minimum number of replicates, do not necessarily encompass the variety of equipment in use throughout the country and the large variability of exposures among handlers. While data from PHED provides the best available information on handler exposures, it should be noted that some aspects of the included studies (e.g., duration, acres treated, pounds of active ingredient handled) may not accurately represent labeled uses in all cases.

The PHED data used for the mixer/loader for lawn treatment, and granular bait application (hand, belly grinder and push-type spreader) scenarios in residential settings are representative of the chlorpyrifos uses as the surrogate data were monitored for the same uses.

Potential exposures and internal doses were calculated using unit exposures (i.e., normalized to amount of active ingredient handled -- mg/lb ai handled) from both passive dosimetry and biological monitoring data extrapolated to be representative of the maximum rates on the label (in some instances to typical rates). The normalized exposure data are extrapolated by multiplying by the amount of chlorpyrifos handled per day (i.e., lb ai/day). The amount of chlorpyrifos assumed handled per day was derived from the various application rates and the number of acres (or gallons of spray solution) that could be applied in a single day. Dermal and inhalation margins of exposure (MOEs) are presented separately along with a combined total MOE.

4.4.1.2 Occupational Handler Risk Characterization

A summary of the short- and intermediate-term risks estimates for PPE and engineering controls is presented in Table 9 for agricultural uses. Table 9 also provides a summary of the range of application rates assessed for chlorpyrifos. Table 10 presents a summary of the short-, intermediate, and long-term risk estimates for LCOs/PCOs at non-agricultural use sites, such as residential and recreational settings.

MOEs for occupational handlers were derived by dividing the appropriate NOAEL, shown on Table 2, by the daily dermal or inhalation exposure estimate. As noted previously, the short-term dermal NOAEL of 5 mg/kg/day is from a dermal rat study, and therefore, no dermal absorption adjustment is necessary. However, both the intermediate- and long-term dermal NOAELs of 0.03 mg/kg/day are based on the weight of evidence from 5 oral toxicity studies in dogs and rats for plasma and red blood cell cholinesterase inhibition, and consequently, dermal exposures were adjusted to absorbed dermal doses using an 3% dermal absorption factor. Inhalation exposure estimates were compared directly to the short- and intermediate-term inhalation NOAEL of 0.1 mg/kg/day, and to the long-term NOAEL of 0.03 mg/kg/day based on the weight of evidence from 5 oral studies in dogs and rats, assuming inhalation absorption is 100% of oral absorption. In evaluating biomonitoring data, which represents total chlorpyrifos exposure via dermal, inhalation and oral exposure, an adjusted absorbed dermal NOAEL of 0.15 mg/kg/day was used (i.e., 5 mg/kg/day *0.03) to estimate MOEs because most

of the total exposure is from the dermal route. Details of this assumption are presented in the HIARC report (D. Smegal April 6, 2000, HED doc no. 014088). For occupationally exposed workers, MOEs >100 (i.e., 10x for interspecies extrapolation and 10x for intraspecies variability) do not exceed HED's level of concern. MOEs below this level would represent a risk concern. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition).

Agricultural and/or Ornamental/Greenhouse Uses

The results of the short-term handler assessments as shown on Table 9 indicate that only 1 of the 16 potential exposure scenarios did not provide at least one application rate with a total MOE(s) greater than or equal to 100 at either the maximum PPE (i.e., coveralls over long pants, long sleeved shirts, and chemical resistant gloves while using open systems) or using engineering controls (i.e., closed systems). There are no data, chemical-specific or surrogate, to assess 3 of the 16 scenarios. For specific details and calculations of inhalation, dermal, and total exposures and MOEs see the attached memorandum from T. Leighton to D. Smegal/M. Hartman, D263893, June 2000. In the majority of cases, it is dermal exposure rather than the inhalation exposure driving the total MOEs.

Within the other 12 scenarios, not all of the application rates/crops have MOEs greater than or equal to 100. More specifically, the total dermal and inhalation MOEs for the 12 scenarios evaluated range from 6 to 10,000. In total, 56 iterations of potential exposures and total MOEs were calculated for the various application rates. Based on the maximum level of protection (i.e., various levels of PPE or engineering controls) 2 MOEs are estimated to be less than 10; 6 MOEs are between 10 and 50; 9 MOEs between 50 and 100 and 39 of the MOEs are greater than 100. There are insufficient information (e.g., dermal and inhalation exposure data) to assess the seed treatment uses, dip applications (e.g., preplant peach root and nursery stock), and dry bulk fertilizer applications to citrus orchard floors. These scenarios are of concern given the results from the other scenarios assessed, and HED has requested data for these uses. Fourteen of the scenarios were based on data obtained from five chemical-specific studies submitted by DAS. Of the 14 MOEs calculated using the biological monitoring results, only two reach the target MOE of 100 using PPE. The test subjects' absorbed dose levels indicate the need for additional risk mitigation measures such as closed systems for loading liquids and enclosed cabs for groundboom and airblast applicators. The results and discussion for each of the 16 exposure

scenarios are presented in greater detail in attached memorandum from T. Leighton to D. Smegal/M. Hartman, D263893, June 2000.

The agricultural handler assessments are believed to be reasonable high end representations of chlorpyrifos uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- extrapolating exposure data by the amount of a.i. handled or applied; and

- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the handlers.

Occupational/Non-Agricultural Uses (e.g., Residential/Recreational Settings)

The following scenarios (by number presented on Table 10) result in total MOEs that exceed HED's level of concern (i.e., MOE less than 100 for LCOs/PCOs):

(1) Indoor Crack and Crevice Treatment by a PCO;

(2) Broadcast Turf Treatment by a LCO (intermediate and long-term applicator/ mixer/loader);

(3) Golf Course Treatments by workers (maximum label rate of 4 lb ai/acre for: mixer/loaders of liquids, and mixer/loaders and applicators for greens and tees) and typical and maximum label rates of 1 and 4 lb ai/acre for groundboom applicators);

(5) Application of Insecticidal Dust Products by a worker;

(6) Application of Granular Formulations by a LCO by hand;

(7) Application of Granular Formulations by a LCO with a belly grinder;

(8) Application of Granular Formulations by a LCO with push-type spreader;

(9) Termiticide Treatments for Pre-Construction by a PCO;

(10) Termiticide Treatments for Post-Construction by a PCO; and

(13) Mosquitocide mixer/loader or applicator for aerial applications of more than 30 days, even with engineering controls

The following scenario results in a total MOE greater than or equal to 100 that does not exceed HED's level of concern for occupational pesticide handlers in residential settings:

(2) Mixer/loader of lawn care products wearing PPE (total MOEs 100-820);

(3) Golf Course Treatments by workers (typical label rate of 1 lb ai/acre for: mixer/loaders of liquid and wettable powders, and mixer/loaders and applicators for greens and tees; maximum label rate of 4 lb ai/acre for mixer/loaders of wettable powders) (total MOEs 100-400).

(13) Workers who mix/load or apply chlorpyrifos for aerial mosquitocide applications of less than 30 days with the use of engineering controls (closed systems)(total MOEs 160-240); and

(13) Workers who mix/load or apply chlorpyrifos for ground-based fogger mosquitocide applications up to several months with the use of PPE and/or engineering controls (total MOEs 100-560).

The results of the LCO/PCO handler assessment in residential/recreational settings for short-, intermediate and/or long-term exposure scenarios indicate that most of the MOEs are less than 100, and therefore exceed HED's level of concern. Exposure for four of the scenarios were estimated based on chemical-specific biomonitoring studies submitted by DAS (i.e., indoor crack and crevice treatment, broadcast turf application, and pre- and post-construction termiticide treatment) in which the LCOs/PCOs wore label-specified PPE, or PPE in addition to that specified on the labels. Several of these studies did not represent the maximum label application rates, or only evaluated exposures for a few hours (i.e. 1-3 hours) of the work day, and consequently could underestimate exposures and risks to LCOs/PCOs. Overall, the exposures and

risks for LCOs/PCOs based on the chemical-specific biomonitoring studies are considered to be central tendency estimates because they evaluated less than a full day's exposure at the maximum label rate or they exclude accidental exposure (e.g., exposures resulting from equipment malfunction).

All risk assessments involve the use of assumptions, judgement and available reliable data to varying degrees. Often, the available data are not the ideal data for evaluating potential exposure scenarios. This results in uncertainty in the numerical estimates of risk. Consideration of the uncertainty inherent in the risk assessment process permits better evaluation of the risk assessment and understanding of the human health impacts. Risks estimates may be overestimated or underestimated to varying degrees. Table 10 characterizes the exposure and risk estimates as low-end, central-tendency and high-end based on the assumptions used in the assessment, and identifies the most significant uncertainties.

4.4.2 Occupational Postapplication Exposure Scenarios

EPA has determined that there is potential exposure to persons entering treated sites (e.g., scouts and harvesters) after application is complete. Postapplication exposure data were required during the chlorpyrifos Data Call In (DCI) of the reregistration process, since, at that time, one or more toxicological criteria had been triggered for chlorpyrifos.

4.4.2.1 Occupational Postapplication Exposure Data and Assumptions

Multiple chemical-specific postapplication exposure studies were also conducted by the registrant and submitted to the Agency. These studies included biological monitoring and passive dosimetry data, along with dislodgeable foliar residue (DFR) data. Data were submitted by DAS for sugar beets, cotton, sweet corn, almonds, pecans, apples, citrus, cauliflower, and tomatoes. The residue decline for these crops indicate that chlorpyrifos quickly dissipates in the first few days after application and then the decline is more subtle. For instance, in most of the crops monitored, the half life of chlorpyrifos for the first part of the curve [i.e., 0 to 7 days after treatment (DAT)] is less than 1 day. However, the second part of the decline curve exhibits a half life of more than 10 days using data from sampling intervals of 7 up to 43 days after treatment (DAT). Based on the initial rapid dissipation of chlorpyrifos as shown in the DFR studies, most of the crops were analyzed using the first part of the decline curve for the short-term endpoint (i.e., up to 1 month) to

establish the restricted-entry interval (REI). The second part of the decline curve was used to assess the intermediate-term duration to assure that workers exposed in treated fields for 1 to 6 months are adequately protected. If the intermediate-term MOEs at the initially assessed short-term REI were less than 100, then the intermediate-term MOEs were used to determine the appropriate length of the REI.

Specific transfer coefficients were also monitored and submitted for citrus harvesting, citrus tree pruning, cauliflower scouting, and tomato scouting. Additional transfer coefficients for other crops/activities are currently being researched by the Agricultural Reentry Task Force (ARTF). In the mean time, HED's standard values for transfer coefficients are used to estimate potential reentry exposure because the ARTF data are not available. Once available, the ARTF data may impact the REIs for tree nuts, tree fruits, and cauliflower. In addition, chemical-specific DFR data are not available for all crops that are potentially treated with chlorpyrifos. Therefore, the assessment of postapplication exposures in this document is based on a grouping of activities associated with various representative crops. The potential for dermal contact during postapplication activities (e.g., harvesting) is assessed using a matrix of potential dermal contact rates by activity and associated crops with groupings of "low", "medium", and "high". In addition to this matrix, citrus, cauliflower, tree nuts and tree fruits are assessed separately. Table 11 summarizes the crops characterized as "low", "medium", and "high".

Maintenance workers and mowers for golf courses were also considered in this assessment and were considered to contact treated turf the day of treatment for short-term durations (i.e., less than 30 days). Although the golf course workers may be working up to 12 months a year, chlorpyrifos levels on the turf will not be available for an appreciable length of time (e.g., residues declining, irrigation, mowing of the turf).

4.4.2.2 Occupational Postapplication Risk Characterization

The results of the short- and intermediate-term postapplication assessments indicate that REIs need to be established. The REIs are presented on Tables 12 and 13. The REIs range from 24 hours for the crop grouping matrix to 10 days for harvesting cauliflower. In short, REIs are 24 hours for all crops except the following: cauliflower (10 days), all nut trees (2 days), all fruit trees (4 days) and citrus (5 days). The timing of the applications are noteworthy because most

of the applications to trees are to the bark during the dormant to early season. There is insufficient information (e.g., timing of applications -- dormant/bark versus foliar treatments) and exposure data to assess postapplication activities for ornamental and soil incorporated uses. The data needed to assess these areas include ornamental dislodgeable foliar residues in greenhouses and biological monitoring data for reentry into areas with soil directed applications. Details of this assessment are presented in memorandum from T. Leighton to D. Smegal/M. Hartman, June 2000, D263893.

Postapplication risks to golf course workers during mow/maintenance activities are presented on Table 14. The short-term MOEs are above 100 (MOE 110 to 210) and therefore, do not exceed HED's level of concern, even at the maximum label rate of 4 lb ai/acre. These risks are conservative because they assume contact with golf course turf the day of treatment.

The occupational postapplication assessments are believed to be reasonable high end representations of chlorpyrifos uses. There are, however, many uncertainties in these assessments. The uncertainties include but are not limited to the following:

- extrapolating exposure and DFR data by the amount of active ingredient handled or applied;
- not all of the exposure data are of high confidence because of the lack of replicates and/or inadequate QA/QC in the studies;
- translating crop-specific DFR data to assess other crops; and
- application timing in comparison to actual potential postapplication exposure scenarios.

These uncertainties are inherent in most pesticide exposure assessments. The conservative nature of the assessments, however, are believed to be protective of the worker.

4.4.3 Residential Handler Exposure

Potential chlorpyrifos residential handler exposures can result from treatment of turf and ornamental plants, as well as indoor use (i.e., for cockroaches, carpenter ants, etc), and structural pest control (i.e., termites). Residential handler exposures to chlorpyrifos can occur via dermal and inhalation routes during handling, mixing, loading and applying activities. All residential handler exposure durations are classified as short-term (1-30 days). As noted previously, in 1997 DAS agreed to work with EPA in

limiting household consumer use to only products packaged as ready-to-use in order to minimize exposure to concentrates that require mixing.

4.4.3.1 Residential Handler Exposure Scenarios

EPA has determined that there is potential exposure to residents during application of chlorpyrifos products. Based on residential use patterns, nine major residential/non-occupational exposure scenarios (by number presented on Table 10) were identified and evaluated for chlorpyrifos:

(1) indoor crack and crevice treatment using an aerosol can;

(2) broadcast turf mixing/loading/application using either a hose end sprayer or a low pressure hand wand;

(4) application of a 0.5% ready-to-use formulated product in a screw top bottle;

(5) application of an insecticidal dust product using a shaker can or bulbous duster;

(6) application of granular formulation by hand;

(7) application of granular formulation with a belly grinder;

(8) application of granular formulation with a push-type spreader;

(11) paintbrush application to wood for an insect infestation; and

(12) treatment of ornamentals (mixing/loading/application) using a low pressure hand wand.

4.4.3.2 Residential Handler Exposure Data Sources and Assumptions

For most cases, residential handler exposure assessments were completed by HED assuming an exposure scenario for residents wearing the following attire: short-sleeved shirt, short pants, shoes and socks, and no gloves or respirator. The only exception is the application of a ready-to-use formulated product, which was evaluated based on a chemical-specific biomonitoring study in which the volunteers wore long pants. Daily unit exposure values were obtained from the Draft Standard Operating Procedures (SOPs) for Residential Exposure Assessments (December 1997) or PHED. Eight of the nine scenarios were evaluated based on data obtained from PHED.

For broadcast turf application, the area treated per day was assumed to be 0.5 acre for hose end sprayer and 1000 ft^2 for spot treatment using a low pressure hand wand or hand application of a granular formulation. Recent lawn size survey data suggest that up to 0.5 acre lawn size represents 73% of 2300 respondents, while nearly 16% of the respondents had lawn sizes that ranged from 0.57 to 1 acre (Outdoor Residential Use and Usage Survey and National Gardening Association Survey 1999). For application of the granular formulation with a belly grinder or push-type spreader, it was assumed that an average of 0.97 lbs active ingredient was handled (i.e., 0.5 acre at 2 lb ai/acre), based on a chemical-specific study of a granular formulated product and the average of 55 replicates from the studies cited in PHED for this use pattern. For a number of scenarios, multiple evaluations were conducted using application rates less than the maximum label rate, or application using different equipment or methods (i.e., ornamental treatment via low pressure hand wand and hose-end sprayer, and granular application via hand, belly grinder and push-type spreader) to assist in risk mitigation and management decisions.

4.4.3.3 Residential Handler Risk Characterization

A summary of the short-term risk estimates, method of evaluation and risk characterization/uncertainties for residential handlers is presented on Table 10. MOEs for residential handlers were derived by dividing the appropriate short-term NOAEL, shown on Table 2, by the daily short-term dermal or inhalation exposure estimate. As noted previously, the short-term dermal NOAEL of 5 mg/kg/day is from a dermal rat study, and therefore, no dermal absorption adjustment is necessary. For inhalation, the short-term

NOAEL is 0.1 mg/kg/day based on two inhalation studies conducted in rats. Evaluation of adult biomonitoring data was conducted two ways, first the total chlorpyrifos dose was compared to an adjusted dermal NOAEL of 0.15 mg/kg/day (i.e., 5 mg/kg/day * 0.03 dermal absorption), because based on available data the majority of exposure is via the dermal route. In addition, HED segregated the total biomonitoring dose into dermal, inhalation, and oral, for comparison with the route-specific toxicity endpoints.

For residential applicators, MOEs > 1000 (i.e., 10x for interspecies extrapolation, 10x for intraspecies variability and 10x for the FQPA factor) do not exceed HED's level of concern. MOEs below this level would represent a risk concern. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition).

The results of the residential handler assessment for short-term exposure scenarios indicate that all nine scenarios evaluated have total dermal and inhalation MOEs that exceed HED's level of concern defined by a target MOE of 1000. The residential handler MOEs ranged from 3 to 900 for dermal risk, from 120 to 57,000 for inhalation risk, and from 3 to 880 for total dermal and inhalation risk for the maximum, typical and even minimum label-recommended application rates. Dermal exposure contributes most to total exposure. For a number of scenarios, multiple evaluations were conducted using application rates less than the maximum label rate, or application using different equipment or methods (i.e., ornamental treatment via low pressure hand wand and hose-end sprayer, and granular application via hand, belly grinder and push-type spreader, spot treatment for crack and crevice). These additional analyses were conducted to provide information for risk mitigation and management decisions. The following scenarios (by scenario number shown in Table 10) result in total MOEs that exceed HED's level of concern (i.e., MOE < 1000) for the typical and/or maximum application rate:

(1) indoor crack and crevice treatment using an aerosol can;

(2) broadcast turf mixing/loading and application using either a hose end sprayer or a low pressure hand wand (spot treatment);

(4) Application of a 0.5% ready to use formulated product in a screw top bottle;

(5) application of an insecticidal dust product using a shaker can

or bulbous duster;

(6) application of granular formulation by hand;

(7) application of granular formulation with a belly grinder;

(8) application of granular formulation with a push-type spreader;

(11) paintbrush application to wood for an insect infestation; and

(12) mixing/loading and treatment of ornamentals using a low pressure hand wand.

As noted previously, all risk assessments involve the use of assumptions, judgement and available reliable data to varying degrees. Often, the available data are not the ideal data for evaluating potential exposure scenarios. This results in uncertainty in the numerical estimates of risk. Consideration of the uncertainty inherent in the risk assessment process permits better evaluation of the risk assessment and understanding of the possible human health impacts. Risks estimates may be overestimated or underestimated to varying degrees. Table 10 characterizes the exposure and risk estimates as low-end, central-tendency and high-end based on the assumptions used in the assessment, and identifies the most significant uncertainties.

4.4.4 Residential/Recreational Postapplication Exposures and Risks

EPA has determined that there are potential postapplication exposures to residents/individuals entering treated areas both indoors following residential/commercial/institutional treatment (i.e., homes, schools, day care centers, etc) for cockroaches, termites or other insects and outdoors following turf treatment (i.e., homes, schools, parks, playgrounds, ball fields, etc) or mosquitocide use. In addition, there is a potential for inadvertent oral exposure to children from eating chlorpyrifos-treated soil, grass and/or granules, or placing their fingers in their mouths. For residential postapplication activities, the exposure duration is expected to be short-, intermediate- and long-term (1 days to several years) depending on the scenario. Adolescent and adult golfers were considered to contact treated turf the day of treatment for short-term durations (i.e., less than 30 days). Details of this assessment are presented in a memorandum from D. Smegal/T. Leighton to M. Hartman, June 2000, D266562.

4.4.4.1 Postapplication Exposure Scenarios

HED identified a total of eleven scenarios likely to result in postapplication exposures to residents/recreational users, and quantitatively evaluated the following ten scenarios:

(1) Indoor Crack and Crevice Treatment of kitchen and bathroom (inhalation exposure in treated room);

(2) Indoor Crack and Crevice Treatment of other rooms (dermal and oral exposure from deposition in untreated room based on registrant data);

(3) Pet Collar Products;

(4) Termiticide Treatments for Basement, Plenum, Slab and Crawlspace Construction Homes;

(6) Broadcast Lawn Treatment Using a Liquid Spray;

(7) Broadcast Lawn Treatment Using a Granular Formulation;

(8) Golf Course Exposure (adolescent and adult golfer);

(9) Aerial and ground-based fogger adult mosquitocide application;

(10) Yard and Ornamental Spray Products, and

(11) Perimeter treatment of residence.

An additional scenario, insecticidal dust product use (scenario 5) was considered, but could not be quantitatively evaluated due to an absence of chemical-specific information and residential SOPs. HED requests exposure data for this, as well as all other scenarios not evaluated.

HED is in the process of revising the Residential Exposure Assessment SOPs. This process may identify specific areas of further concern with respect to chlorpyrifos and exposure to the general population. For example, some of the secondary exposure pathways that EPA is currently examining include exposures resulting from residue tracked into homes from outdoor use, indoor dust, and spray drift. In a recent study, polycyclic aromatic hydrocarbons (PAHs) that are abundant in house dust were shown to increase the toxicity of chlorpyrifos in vitro, particularly at low levels (i.e., 2-50 FM

PAHs with 1-180 nM chlorpyrifos-oxon, a metabolite of chlorpyrifos that inhibits acetyl cholinesterase) (Jett et al. 1999). Currently, there are no SOPs available to evaluate these potential exposure pathways. These scenarios however, may be evaluated in the future pending revisions to the residential SOPs.

4.4.4.2 Data Sources and Assumptions for Postapplication Exposure Calculations

HED evaluated four of the eleven residential postapplication exposures scenarios based on chemical-specific studies submitted by DAS (i.e., crack and crevice treatment of the kitchen and bathroom (1), broadcast treatment of turf with chlorpyrifos spray (6) and granules (7), and termiticide treatment (4)). Three of these studies (crack and crevice, and two lawn studies) included biomonitoring of the urinary metabolite 3,5,6-TCP, in addition to environmental measurements to quantify chlorpyrifos exposures. In the absence of chemical-specific data, the other exposures (scenarios 2, 3, 8, 9 and 11) were evaluated using the equations and assumptions presented in the Draft SOPs for Residential Exposure Assessments guidance document or revised assumptions from the SOPs to be released in 2000 (i.e., indoor crack and crevice treatment of other rooms, mosquitocide uses, golfer exposures, pet collar uses and perimeter treatments), which are generally considered to result in high-end exposure estimates, except for the crack and crevice treatment. Scientific literature studies, the AgDrift Model and assumptions from the updated and Draft Residential SOPs were used to evaluate adult mosquitocide uses.

4.4.4.3 Residential/Recreational Postapplication Risk Characterization

A summary of the postapplication risk estimates, method of evaluation, and risk characterization/ uncertainties is presented in Table 15. MOEs for residential/recreational postapplication exposures were derived by dividing the appropriate NOAEL, shown on Table 2, by the daily dermal, inhalation or oral exposure estimate. As noted previously, biomonitoring data was evaluated two ways, first the total chlorpyrifos dose was compared to an adjusted dermal NOAEL of 0.15 mg/kg/day (i.e., 5 mg/kg/day * 0.03 dermal absorption), because the majority of exposure is via the dermal route. In addition, because there is no scientifically valid method to extrapolate from adult biomonitoring data to child exposure, HED segregated the total biomonitoring dose into dermal, inhalation, and oral exposure estimates, for comparison with the route-specific

toxicity endpoints. This extrapolation was conducted only for the post application exposures from lawn treatment. For residents, the acceptable MOE is 1000 (i.e., 10x for interspecies extrapolation, 10x for intraspecies variability and 10x for the FQPA factor). MOEs below this level would represent a risk estimate of concern for the Agency. A total dermal and inhalation MOE was also calculated because there is a common dermal and inhalation toxicity endpoint (i.e., cholinesterase inhibition). For child exposures, oral exposure also contributed to the total MOE. The following scenarios result in MOEs less than 1000, or potential exposures that exceed HED's level of concern:

(1,2) Indoor Crack and Crevice Treatment of kitchen and bathroom (inhalation exposure in treated room, dermal and oral exposure in untreated room);

(3) Pet Collar Products;

(4) Termiticide Treatments for Crawlspace, Basement, Plenum and Slab Construction Homes;

(6) Broadcast Turf Treatment Using a Liquid Spray;

(7) Broadcast Turf Treatment Using Granular Formulation;

(8) Golf Course Exposure (adolescent and adult golfer) following treatment at the maximum rate of 4 lb ai/acre, and

(11) Perimeter Treatments of Residences.

In addition, by analogy, HED evaluated yard and ornamental spray products (Scenario 10) and concluded that these products result in comparable doses and short-term MOEs with the lawn care products based on label uses and application rates. Therefore, use of many of these products is likely to result in MOEs that exceed HEDs level of concern.

The following scenarios result in MOEs greater than 1000 that do not exceed HED's level of concern for post-application residential/recreational exposures:

(8) Golf Course Use (adolescent and adult golfer) following treatment at the typical rate of 1 lb ai/acre; and

(9) Aerial and ground-based fogger adult mosquitocide application.

In conclusion, seven of the nine scenarios evaluated quantitatively have MOEs that are less than 1000, and therefore exceed HED's level of concern. In addition, for post application exposure to children following perimeter applications to homes, it was estimated that more than seven hand-to-mouth events or more than 8 minutes of play on treated turf the day of treatment could result in potential exposures that could exceed the Agency's level of concern (i.e., MOE < 1000). Total MOEs for the residential postapplication exposures that exceed HED's level of concern ranged from 6 to 980. The only postapplication scenario that resulted in a MOE consistently above 1000 was from the aerial and ground-based fogger adult mosquitocide applications (MOEs are 17,000 and 29,000 for children and adults, respectively). In addition, MOEs for adolescent and adult golfers are above 1000 following treatment of golf courses at the typical, or median rate of 1 lb ai/acre (MOEs 1500-2400). A summary of the termiticide postapplication exposure and risk estimates is presented in greater detail below.

As noted previously, all risk assessments involve the use of assumptions, judgement and available reliable data to varying degrees. Often, the available data are not the ideal data for evaluating potential exposure scenarios. This results in uncertainty in the numerical estimates of risk. Consideration of the uncertainty inherent in the risk assessment process permits better evaluation of the risk assessment and understanding of the possible human health impacts. Risks estimates may be overestimated or underestimated to varying degrees. Table 15 characterizes the exposure and risk estimates as low-end, central-tendency and high-end based on the assumptions used in the assessment, and identifies the most significant uncertainties. As noted on Table 15, the exposure and risk estimates based on the chemical-specific studies are generally considered to be reasonable central-tendency estimates (i.e., arithmetic mean, or median exposure was used to calculate risk). Because three of the chemical-specific studies were conducted in adults, conservative assumptions were used to estimate child exposures. However, because adult activity patterns differ from children, i.e., hand-to-mouth activity, some of the registrant-submitted chemical-specific studies could under-estimate a child's exposure (e.g., lawn studies are not designed to reflect any potential for incidental ingestion of residues from treated turf, soil and/or granules).

An additional scenario, postapplication exposures associated with insecticidal dust product use (scenario 5) could not be quantitatively evaluated due to an absence of chemical-specific data or recommended procedures in the Residential SOPs. Nevertheless,

HED has concerns about the use of these products based on the low MOEs calculated for residents or workers that could apply dust products. HED recommends that the registrant provide additional information on the potential post-application residential exposures associated with dust products.

HED identified a number of data gaps for assessing post application exposure, and these data gaps are discussed in Section 6.0.

HED has concerns for the potential for children's exposure in the home as a result of residential and/or agricultural uses of chlorpyrifos. Environmental concentrations of chlorpyrifos in homes may result from residential uses, spray drift, track-in, or from redistribution of residues brought home on the clothing of farm workers or pesticide applicators. Potential routes of exposure for children may include incidental ingestion and dermal contact with residues on carpets/hard surfaces, in addition to inhalation of vapor and airborne particulates. There are several literature studies that quantify the levels of chlorpyrifos in household dust, indoor and outdoor air, dermal wipe (hands) and soil samples. These residues may persist and the resulting exposures are of a potential chronic nature. Currently, there are no SOPs available to evaluate potential exposures from spray drift and track-in. The Agency is currently in the process of revising its guidance for completing these types of assessments. Modifications to this assessment shall be incorporated as updated guidance becomes available. This will include expanding the scope of the residential exposure assessments by developing guidance for characterizing exposures from other sources already not addressed such as from spray drift; residential residue track-in; and exposures to farm worker children.

Termiticide Risk Characterization and Uncertainty Analysis

Because of chlorpyrifos' extensive use as a termiticide, HED has provided a detailed summary of the risks and uncertainties associated with termiticide treatments. The Agency conducted an assessment of termiticide postapplication risks based on a chemical-specific exposure study submitted by DAS. This study collected air measurements from the basement, kitchen and bedroom of 31 homes for up to 1 year following a termiticide treatment. Four types of housing structures were evaluated: basement, plenum, slab and crawlspace. Chlorpyrifos was applied according to the label-recommended rate of approximately 1% active ingredient.

The Agency calculated incremental time-weighted average (TWA) air concentrations for the entire house, assuming an individual could be in any room. Based on this assessment, risks from inhalation exposure was the primary concern. Based on the mitigation plan, the TWA concentrations were normalized to a reduced application rate of 0.5% ai. As part of risk characterization, the Agency evaluated risks for both intermediate and chronic exposures because of uncertainties in the toxicity endpoints for both durations. Details of this analysis are presented in the Occupational/Residential Handler and Post-Application Residential/Non-Occupational Risk Assessment (memo from D. Smegal/T. Leighton, June 2000, D266562). The MOEs are presented on Table 15.

Similar to the dietary assessment, children 1-6 years of age have higher potential exposures than adults, primarily because of to a higher breathing rate per body weight, and data that indicate young children spend more time at home than adults. For children, all the 90-day median MOEs are greater than 1000 (median MOEs range from 1,900 to 3,800), and therefore do not exceed HED's level of concern. However, some of the 1-year median MOEs are below 1000, and therefore exceed HED's level of concern (median MOEs range from 530 to 1,100). As shown on Table 15, the lowest 90-day and 1-year MOEs for an individual house are 440 and 270, respectively.

The median MOEs for adults were greater than 1000 for all housing types for both the 90-day and 1-year analysis, and therefore, do not exceed the Agency's level of concern (MOEs range from 1,800 to 13,000).

There are however, a number of uncertainties in the risk assessment that arise from the following sources: choice of toxicological data used to establish the inhalation toxicity endpoint, chlorpyrifos air concentrations, and exposure assumptions. The most significant uncertainties will be discussed below.

Toxicity Endpoints: There are uncertainties associated with both the intermediate and long-term inhalation NOAELs used to calculate the MOEs. The intermediate-term NOAEL of 0.1 mg/kg/day is based on two 90-day inhalation studies, in which the rats were exposed 6 hours/day, 5 days/week (nose-only) to the highest attainable vapor concentration of chlorpyrifos (287 Fg/m^3). HED could not identify an inhalation LOAEL because no adverse effects were noted at the highest dose tested. Therefore, HED selected an oral LOAEL of 0.3 mg/kg/day to use in the dose-response

assessment. The 3 fold difference between the NOAEL and LOAEL, adds an extra buffer of safety to the intermediate-term inhalation endpoint for a total MOE of at least 3000. Although the inhalation route of exposure is ideal for this assessment, the exposure regimen does not fully mimic the potentially continuous inhalation exposure for children associated with a termiticide treatment (i.e., up to 20 hours/day).

The long-term NOAEL of 0.03 mg/kg/day is based on oral animal studies that observed cholinesterase inhibition at 0.2 to 0.3 mg/kg/day (the LOAEL). HED notes that the large difference between the NOAEL and LOAEL (i.e., factor of 6.7 to 10), adds an extra buffer of safety to the long-term inhalation endpoint. Therefore, relative to the LOAEL, the MOE is actually at least 6,000 to 10,000 for a target MOE of 1000. In addition, there are significant uncertainties associated with route-to-route extrapolation due to differences in pharmacokinetics. Following oral exposure, chlorpyrifos is absorbed in the gastrointestinal tract and is transported to the liver, where it can undergo biotransformation to a potent cholinesterase inhibitor (chlorpyrifos-oxon), and be further detoxified. However, following inhalation exposure, chlorpyrifos is absorbed directly into the systemic circulation and initially bypasses the liver. These pharmacokinetic differences may play an important role in the route-specific toxicity of chlorpyrifos. In the absence of inhalation pharmacokinetic data, it is difficult to predict whether use of an oral NOAEL would over- or under-estimate inhalation risks.

Air Concentrations: There are also a number of uncertainties associated with the chlorpyrifos air concentrations used to assess termiticide risks, which affect both the 90 day and 1 year MOEs calculations. Measured chlorpyrifos air concentrations may be overestimated because of use of other chlorpyrifos-containing products. For example, more than half (55% or 17/31) of the homes in the DAS study had detectable chlorpyrifos air concentrations prior to termiticide treatment, indicating that residents may have used other chlorpyrifos products in the home, or had a previous chlorpyrifos termiticide treatment. Several studies in the scientific literature reported chlorpyrifos air concentrations up to 8 years following termiticide treatments (Wright et al. 1988, 1994). However, these studies did not control for use of other chlorpyrifos products (i.e., lawn treatment, flea control, or other indoor uses, etc) (personal communication by D. Smegal with G. Dupree 5/17/2000), and therefore, may also overestimate potential exposures and risks.

In addition, spills inside the home can contribute to higher airborne concentrations of chlorpyrifos. In the DAS study, one of the

homes had elevated basement air concentrations because of a spill. The elevated basement measurements were excluded from the analysis (i.e., only kitchen and bedroom air data were used). This is considered reasonable because spills are likely to be an infrequent occurrence, and because pest control operators (PCOs) are trained to promptly clean spills that occur during application. However, possible applicator error, unreported, undetected or unremediated spills can contribute to air concentration measurements.

The available data suggest that temperature influences indoor chlorpyrifos concentrations resulting from termiticide treatments (i.e.,warmer temperatures are associated with higher concentrations). In the DAS study, 26 of 31 homes were from the South or warm climates. Therefore, it is possible that the air concentrations used in this assessment represent high-end estimates, that could overestimate exposures for treated houses in more temperate climates.

There are uncertainties associated with the incremental TWAs air concentration calculations. Based on the mitigation plan, HED calculated the incremental TWAs by adjusting the air measurements associated with a 0.7-1% ai product application to 0.5% assuming that there is a linear relationship between percent ai and resulting air concentrations. This assumption is considered reasonable, although it could under- or over-estimate the air concentrations associated with 0.5% a.i. product application. In addition, the 1-year incremental TWA concentration may be overestimated for two basement homes, because one year air concentration measurements were not available. HED assumed the 90 day air concentration remained constant from 90 to 365 days. This assumption only impacts two basement homes (B1 and B2), both of which had 1 year MOEs less than 1000, but 90 day MOEs greater than 1000.

Exposure Assumptions. The assumptions used to estimate exposures are based on USEPA recommended values (Exposure Factors Handbook), and are designed to be conservative for the majority of the population. These estimates could be conservative for children that do not spend their entire day at home (i.e., those that attend day-care, pre-school, and/or school). This assessment assumed that children aged 1-6 years are exposed to chlorpyrifos air concentrations in a treated home for 20 hours/day, 7 days/week, for up to 1 year.

Summary: In summary, HED believes that individuals are unlikely to experience adverse health effects from termiticide use of chlorpyrifos, even though a few of the child MOEs are below 1000.

Based on the uncertainties described above, the 90 day risk estimates may be underestimated, while the 1 year risk estimates may be overestimated. Overall, HED believes that the risk estimates are bounded by the ranges presented in Table 15. As shown on Table 15, the lowest 90-day and 1-year MOEs for an individual house are 440 and 270, respectively and the highest estimates are 13,000 and 9,500, respectively. Although some MOEs are less than 1000, there is an additional 3 to 10 fold buffer because of the difference between the NOAEL and the LOAELs. In addition, a number of conservative assumptions were incorporated into these MOEs, such as assuming that all children spend 20 hours/day, 7 days/week for up to 1 year in a treated home.

Mitigation measures will further reduce exposures and risk. For example, the removal of whole house barrier treatment addressed the exposures of most concern. It is expected that the limited spot and localized treatment, and pre-construction treatments would represent less exposure and risk. Based on the mitigation plan, and best professional and scientific judgement, HED concludes that the termiticide risk does not raise a concern and that individuals are unlikely to experience adverse health effects from termiticide treatments conducted according to the label. This conclusion is based on the conservative assumptions, the risk mitigation measures, coupled with the uncertainties of the toxicity endpoints and the air measurements.

Table 9
Exposure Variables and MOEs for Agricultural Uses
(Including Non Worker Protection Standard Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario#)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term PPE MOEs			Short-Term Eng. Control MOEs		
				Dermal	Inhalation	Total	Dermal	Inhalation	Total
Mixer/Loader Exposure									
Mixing/Loading Liquids for Aerial/Chemigation Application (1a)	Yes MRID No. 44739302	1.5 cranberries, corn	350	39	56	23	78	160	52
		3.5 citrus (d)	100	59	83	34	120	240	78
Mixing/Loading Liquids for Groundboom Application (1b)	Yes MRID No. 42974501	1.5 predominant max	80	170	240	100	Target MOE reached at PPE		
		5.0 tobacco max	80	51	73	30	100	210	69
		2 Sodfarm (includes tobacco/ potatoes)	80	130	180	75	250	530	170
		4 Sodfarm	80	64	91	38	130	260	86
		8.0 sodfarm fire ants	10	260	360	150	Target MOE reached at PPE		
Mixing/Loading Liquids for Airblast Application (1c)	Yes MRID No. 43138102	2.0 predominant max such as Fruits & Nuts	40	260	360	150	Target MOE reached at PPE		
		6.0 citrus	20	170	240	100	Target MOE reached at PPE		
Mixing WP for Aerial/Chemigation Application (2a)	No	2.0 predominant max (orchards)	350	DAS is not supporting the open bag formulation for the WP			51	42	23
		3.5 citrus (d)	100				100	83	46
Mixing WP for Groundboom Application (2b)	Yes MRID No. 42974501	1.0 predominant max (brassica)	80				450	360	200
		4.0 soil treatment ornamentals outdoors	10				890	730	400
		1.3 & 3.0 Sodfarm	80				340 / 150	280 / 120	150 / 67

Table 9
Exposure Variables and MOEs for Agricultural Uses
(Including Non Worker Protection Standard Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario#)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term PPE MOEs			Short-Term Eng. Control MOEs		
				Dermal	Inhalation	Total	Dermal	Inhalation	Total
		8.0 sodfarm fire ants (harvest only)	10				4500	3600	200
Mixing WP for Airblast Application (2c)	No	2.0 predominant max	40				450	360	200
		6.0 citrus	20				300	240	130
Loading Granulars for Aerial Application (3a)	No	1.95 maximum aerial rate	350	150	30	25	3000	300	270
Loading Granulars for Ground Application (3b)	Yes MRID No. 44483501 (3b and 8)	1.0 typical corn	80	1300	260	210	Target MOE reached at PPE		
		2.0 max corn	80	640	130	110	Target MOE reached at PPE		
		3.0 maximum ground rate (tobacco)	80	430	86	71	8600	860	780
Applicator Exposure									
Aerial (Spray) -- Enclosed Cockpit (4a)	No	2.0 orchards	350	No Open cockpit data available			100	150	60
		3.5 citrus (d)	100				200	290	120
Aerial (Granulars) -- Enclosed Cockpit (4b)	No	1.95	350	No Open cockpit data available			320	8	8
Groundboom Tractor (5)	Yes MRID No. 42974501	1.5 predominant max	80	The biological monitoring results (Table A4) indicate that open cabs provide insufficient protection . Therefore, only the enclosed cab MOEs are presented.			580	1400	410
		5.0 tobacco max	80				180	410	120
		4 Sodfarms	80				220	510	150
		8.0 sodfarm fire ants	10				880	2000	610

Table 9
Exposure Variables and MOEs for Agricultural Uses
(Including Non Worker Protection Standard Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario#)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term PPE MOEs			Short-Term Eng. Control MOEs		
				Dermal	Inhalation	Total	Dermal	Inhalation	Total
Airblast Applicator (6)	Yes MRID No. 43138102	2.0 predominant max	40	The biological monitoring results indicate that open cabs are insufficient.			230	190	110
		6.0 citrus	20				150	130	70
Tractor-Drawn Granular Spreader (7)	Yes MRID No. 44483501 (3b and 8)	1.0 typical corn	80	1000	360	270	Target MOE reached at PPE		
		2.0 max corn	80	520	180	140	Target MOE reached at PPE		
		3.0 maximum ground rate (tobacco)	80	350	120	90	690	130	110
Seed Treatment (8)	No	No Data	No Data	No Data			No Data		
Dip Application (Preplant Peaches) (9)	No	No Data	No Data	No Data			No Data		
Flagger Exposure									
Spray Applications (10)	No	2.0 predominant max	350	50	140	37	2300	1400	880
		3.5 citrus (d)	100	100	290	74	4500	2900	1800
Granular Applications (11)	No	1.95	350	320	340	170	Target MOE reached at PPE		
Mixer/Loader/Applicator Exposure									
Backpack Sprayer (12)	Yes MRID No. 43027901	0.0417 lb ai/gal predominant max / 0.08 lb ai/gal bark beetle treatment / 0.03 lb ai/gal stump treatment	40 gal/day	130 / 68 / 180	700 / 360 / 970	110 / 58 / 150	Target MOE reached at PPE, except for the higher concentration for the beetle bark treatment		
		3.5 citrus bark	1 A/day	63	330	53	Not feasible		
		0.039 lb ai/gal /750 ft2	1000 ft2	4200	22000	3500	Target MOE reached at PPE		

Table 9
Exposure Variables and MOEs for Agricultural Uses
(Including Non Worker Protection Standard Ornamental Uses) of Chlorpyrifos

Exposure Scenario (Scenario#)	Are Biological Monitoring Data Available? (a)	Application Rates (lb ai/acre) (b)	Daily Acres Treated (c)	Short-Term PPE MOEs			Short-Term Eng. Control MOEs		
				Dermal	Inhalation	Total	Dermal	Inhalation	Total
Low Pressure Handwand (13)	Yes MRID No. 43027901	0.0417 lb ai/gal predominant max / 0.08 lb ai/gal bark beetle treatment / 0.03 lb ai/gal stump treatment	40 gal/day	570 / 300 / 790	700 / 360 / 970	310 / 160 / 440	Target MOE reached at PPE		
		3.5 citrus bark	1 A/day	270	330	150	Target MOE reached at PPE		
		0.039 lb ai/gal/ 750 ft2 animal prem.	1000 ft2	18000	22000	10,000	Target MOE reached at PPE		
High Pressure Handwand (greenhouse uses) (14)	Yes MRID No. 43027901	Min. 0.0033 lb ai/gal	1000 gal/day	66	88	38	Not feasible		
		Max. 0.0066 lb ai/gal		33	44	19	Not feasible		
Hydraulic Hand-held Sprayer for Bark / Pine Seedling Treatment (15)	No	3.5 citrus bark	10	16	100	14	Not feasible		
		0.08 lb ai/gal bark beetle treatment / 0.16 lb ai/ gal pine seedling treatment /	1,000	14 / 7	88 / 44	12 / 6	Not Feasible		
		0.039 lb ai/gal /750 ft2 animal prem	10000 ft2	2,200	13,000	1,900	Target MOE reached at PPE		
Dry Bulk Fertilizer Impregnation	No	1.0 lb ai / 200 lb fertilizer / acre	No Data	No Data			No Data		

(a) Biological monitoring data are available from several chemical-specific studies. Although biological monitoring scenarios are available for some of the scenarios as indicated in this table, passive dosimetry data are presented for comparison because insufficient replicates and/or additional risk mitigation measures were necessary.

(b) Application rates are the maximum labeled rates found on EPA Reg. Nos. 62719-38, -221, -245, -34; -79, -72, -166, -220, 34704-66 (Clean Crop Chlorpyrifos 4E -- sodfarm fire ant rate), 499-367 (499-367 is the only greenhouse label identified), and 10350-22 for animal premise treatments. **"Predominant max"** in this table refers to the most **frequently identified maximum** application rate found on the labels for the specific formulation and equipment type. Typical rates are also included to characterize the chlorpyrifos uses. Not all application rates are included for all crops, instead, a cross-section of rates are used to represent the uses of chlorpyrifos.

(c) Daily acres treated are based on HED's estimates of acreage (or gallonage) that would be reasonably expected to be treated in a single day for each

exposure scenario of concern. The sodfarm fire ant rate is restricted on the label for harvest only, therefore, this rate is limited to the amount of sod that may be harvested in a reasonable time frame. Therefore, using the limited data available, approximately 10 acres treated per day are assumed to be the upper range.

(d) The application rates on the Lorsban 4E (EPA Reg. No. 62719-220) and 50W (EPA Reg. No. 62719-39 discontinued as of 1995 and sold as -221) labels indicate that for citrus at the 6.0 lb ai/A rate it is necessary to use 100 to 2,400 gallons per acre dilute spray. Therefore, this rate is not expected to be feasible for an aerial applicator. The label language should be clarified so that the 6.0 lb ai/A rate is for ground only. Additionally, citrus orchards are believed to be relatively small plots and 100 acres per day is assumed in the assessment for aerial applications.

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
(1) Indoor Crack & Crevice Treatment						
Long term PCO Applicator (0.29% Dursban Pro; EPA Reg. 62719-166)	double layer clothes, chemically-resistant boots and gloves, eye protection	Biomonitoring study MRID No. 44444801 (minimum, mean and maximum amount handled)	17 (max) 59 (mean) 5900 (min)	58 (max) 200 (mean) 20,000 (min)	13 (max) 45 (mean) 4500 (min)	Central-tendency risk estimates for applicators; MOEs less than 100 for workers that could handle $0.02 lb ai/day (the mean amount handled in the study). Only two of 15 replicates reflect the maximum label concentration of 0.5% ai. (avg of 0.29% ai was handled in study). Underestimates exposure to workers that mix/load and apply chlorpyrifos because study only evaluated applicators.
Short-term Residential Applicator (EPA Reg 026693-00003 for 1% ai; 239-2619 for 0.5% ai)	SS, SP, no gloves	Residential SOPs (PHED V1.1)	159 (1%) 318 (0.5%) 2540 (spot treatment)	292 (1%) 584 (0.5%) 4700 (spot treatment)	100 (1%) 200 (0.5%) 1600 (spot treatment)	High-end risk estimates for 1% ai; central tendency for 0.5% ai; assumes application of one 16 oz. aerosol can for both; low-end to central tendency risk for spot treatment which assumes 2 oz application of 0.5% ai. product
(2) Broadcast Turf Application (Intermediate and Long-Term for PCOs; Short-Term for Residential Applicators)						
Applicator (1 or 4 lb ai/Acre of Dursban Pro, EPA Reg. 62719-166)	single layer clothes, chemically-resistant knee high boots and gloves, hat (knee high boots not required by label)	Biomonitoring Study MRID No. 44729401 (25% of label maximum rate or adjustment for label-recommended max application rate)	Biomonitoring: 75 (IT&LT) (1 lb ai/acre) Label Max: 20 (IT&LT) (4 lb ai/acre)			Central-tendency risk estimates for 1 lb ai/acre; product applied at 25% of label maximum. High-end risk estimates for 4 lb ai/acre (label maximum for subsurface soil treatment). Study evaluated an average 1.5 hour spray time over a 6 hour work day which may underestimate worker exposure based on TruGreen/ChemLawn data for 193 workers that show an average spray time of 2.75 hours over a 8.75 hour work day.
Mixer/Loader (liquid) (Dursban Pro, EPA Reg. 62719-166)	single layer clothes, gloves	PHED V1.1 (biomonitoring study rate and 25% of maximum label rate)	260-1032	500-1980 (IT) 150 -600 (LT)	170-680 (IT) 100-380 (LT)	Central-tendency to High-end risk estimates; maximum ai handled in study with maximum (4 lb ai/acre) and 25% of maximum label rate (1 lb ai/acre), respectively
	double layer clothes, gloves		350 -1400		200-820 (IT) 100 -420 (LT)	

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
Residential Mixer/Loader/ Applicator Broadcast with Hose End Sprayer (Dursban 1-12 Insecticide EPA Reg 62719-56)	SS, SP, no gloves	Residential SOPs (PHED V1.1) (min and max dilution rates)	6-23	368-1470	6-23	Central-tendency to High-end risk estimates; Low confidence in exposure estimates from PHED V1.1; assumes resident handles 22 gallons of minimally and maximally diluted product
Residential Mixer/Loader/ Applicator Spot treatment with Low Pressure Handwand (Dursban 1-12 Insecticide EPA Reg 62719-56)	SS, SP, no gloves	Residential SOPs	37-150	2490-9960	37-150	Central-tendency to High-end risk estimates; Low confidence in dermal exposure estimates, and medium confidence in inhalation exposure estimates; assumes resident handles 1 gallon of minimally and maximally diluted product to treat 1000 ft^2.
(3) Golf Course Use (Dursban Turf Insecticide; EPA Reg. 62719-35) (Short-term)						
Mixer/Loader (Liquid)	LS, LP, gloves	PHED V1.1	95-380	36-150	26-100	High-end for 4 lb ai/acre and central tendency for 1 lb ai/acre; assumes handling product to treat 40 acres at 1-4 lb ai/acre. Using PHED only 4 lb ai/acre results in MOEs < 100 for liquid mixer/loader (MOE=26). For groundboom applicator, MOE < 100 based on biomonitoring at both 1 and 4 lb ai/acre. HED has more confidence in the biomonitoring results than PHED.
Mixer/Loader (Wettable Powder in water soluble bags)	LS, LP, gloves	PHED V1.1	220-820	180-730	100-400	
Groundboom Applicator	LS, LP, no gloves	PHED V1.1	160-630	59-240	43-170	
		Biomonitoring (MRID 42974501)	15-63		15-63	
Mix/Load/Apply via Handgun (greens/tees) (Liquid)	LS, LP, gloves	PHED V1.1	49-190	130-540	36-140	High-end for 4 lb ai/acre and central tendency for 1 lb ai/acre; assumes handling product to treat 5 acres at 1-4 lb ai/acre. Only 4 lb ai/acre results in MOEs < 100

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
(4) Ready-to-Use 0.5% a.i. Formulated Product (Ortho Ant Stop)						
Short-term Residential Applicator	SS, LP, no gloves	Outdoor Biomonitoring Study MRID No. 44739301	625 (biomonitoring)		625	Central-tendency to high-end risk estimate; assumes resident applies five 24 oz bottles of product/day, however, resident wore long pants and current HED policy is to evaluate exposures for short pants. Risks calculated two ways, one using total exposure based on biomonitoring, and second by comparing estimated route-specific exposure to appropriate toxicity endpoints.
			714	3,400	590	
(5) Insecticidal Dust Product (Shaker Can or Bulbous Duster)						
Residential Applicator (1% ai chlorpyrifos; 2.83 g ai) (EPA Reg. 62719-66, 62719-54, and 192-174)						
Short- term	SS, LP, no gloves	Scientific Literature Study	250	NE	250	Central-tendency to High-end risk estimates; assumes an individual applies a 10 oz can of 1% ai chlorpyrifos dust; neglects inhalation exposure due to an absence of data.
Worker (7% ai chlorpyrifos; 7.91 or 198 g ai) (EPA Reg. 13283-17, Rainbow Kofire Ant Killer)						
Short- term	LS, LP, gloves	Scientific Literature Study	98 (7.9 g) 3.9 (198 g)	NE	98 (7.9 g) 3.9 (198 g)	Central-tendency short term risk assessments for 7.9 and 198 g ai; High-end intermediate-term risk estimates for 7.9 and 198 g ai (based on size of dust container); Neglects inhalation exposure due to an absence of data.
Intermediate term			20 (7.9 g) 0.8 (198 g)	NE	20 (7.9 g) 0.8 (198 g)	

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
(6) Granular Formulation (Hand Application) (EPA Reg. 672719-14, 62719-210) (2 lb ai/acre)						
LCO (intermediate-term)	LS, LP, gloves	PHED V1.1	21	324	20	High-end risk estimates; medium confidence in PHED unit exposure estimates which are based on a single study in which a test subject wearing chemical-resistant gloves spread the granular formulation around the outside of the residence and over 90 percent of the samples contained no detectable material. Therefore, residents also evaluated wearing long pants, long sleeved shirt and gloves. Assumes treatment of 1000 ft^2. Could underestimate exposure because PHED data excludes head and neck area.
	Double layer clothing, gloves		38	324	34	
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	18	327	17	
	LS, LP, gloves		106	330	80	
(7) Granular Formulation (Belly Grinder) (EPA Reg. 672719-14, 62719-210) (2 lb ai/acre)						
LCO (intermediate-term)	LS, LP, gloves	PHED V1.1	8	120	7	Central-tendency risk estimates for worker; High-end risk estimates for residents, except for spot treatment. Low and high confidence in the dermal and inhalation exposure estimates, respectively. Assumes treatment of 0.5 acre at typical rate of 2 lb ai/acre for subsurface feeding insects. Could underestimate exposure because PHED data excludes head and neck area. Workers could treat more than 0.5 acre/day.
	Double layer clothing, gloves		12.5	120	11	
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	3	120	3	
			69 (spot)	36 (spot)	24 (spot)	
(8) Granular Formulation (Push-type Spreader) (EPA Reg. 672719-14, 62719-210)(2 lb ai/acre)						
LCO (intermediate-term)	LS, LP, gloves	PHED V1.1	57	1150	54	Central-tendency risk estimates for worker; High-end risk estimates for residents. Low and high confidence in the dermal and inhalation exposure estimates, respectively. Assumes treatment of 0.5 acre at typical rate 2 lb ai/acre for subsurface feeding insects. Could underestimate exposure because PHED data excludes head and neck area. Workers could treat more than 0.5 acre/day.
	Double layer clothing		100	1150	92	

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
Residential Applicator (short-term)	SS, SP, no gloves	Residential SOPs	120	1150	110	

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
Termiticide Treatments						
(9) Pre-Construction (1.44% chlorpyrifos as Dursban TC) (EPA Reg. 62719-47) (long-term)						
Mixer/Loader/ Applicator (3 hour average exposure)	label-specified PPE: single layer clothes and forearm-length chemically-resistant gloves (forearm length gloves not required by label)	Dosimetry and air monitoring from Registrant Study MRID No. 44589001	19	67	15	Low-end risk estimates for workers that wore double layer of clothing and forearm length gloves not required by the label; Central-tendency risk estimates for workers that wore a single layer of clothing and forearm length gloves; assumes 3 hour exposure, which could underestimate risks to workers exposed > 3 hrs/day, or that use 2% ai to treat utility poles or fences
	double layer clothes (LS,LP, coveralls, rubber boots, and forearm-length gloves) (forearm-length gloves not required by label)		63	67	33	
Tarp puller	with forearm-length gloves (LS,LP, leather and/or rubber boots and hat)	Dosimetry and air monitoring from Registrant Study (1-8 tarps) MRID No. 44589001	170-1300	180-1400	87 (8 tarps) 690 (1 tarp)	Central-tendency risk estimates; assumes workers pull 1-8 tarps/day (7 min/tarp), could underestimate risks to workers who pull > 8 tarps/day (i.e., >1 hr exposure/day). All total MOEs < 100 for 8 tarp/day. Also, workers wore forearm length gloves not required by the label which reduce estimated exposure.
	without gloves (LS,LP, leather and/or rubber boots and hat)		47-370	240-2000	39 (8 tarps) 310 (1 tarp)	
(10) Post-Construction (1% chlorpyrifos as Dursban TC) (EPA Reg. 62719-47) (long-term)						
Mixer/Loader/ Applicator	Label-specified PPE: LS, LP, chemically resistant gloves, hat, eye protection and half face piece respirator in confined spaces; During M/L: 2 layers clothes and chemically-resistant shoes	Biomonitoring: 4.3 MRID No. 44729402 (n=5)	7		7	Central-tendency risk estimate, could underestimate risks for workers that apply 2% ai to treat utility poles or fences
		Dosimetry and air monitoring MRID No. 44729402 (n=14)	12	33	9	Central-tendency risk estimate; excludes worker with higher exposure (10X greater than mean) due to a broken hose

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
(11) Paint Brush (Short-term) (Dursban 1-12 Insecticide, EPA Reg. 62719-56)						
Residential Applicator	SS, SP, no gloves	Residential SOPs; 1 gallon for worst case and 1 quart for typical case	37 (1 gal) 148 (1 qt)	590 (1 gal) 2300 (1 qt)	35 (1 gal) 140 (1 qt)	Central-tendency risk estimates for typical case and high end risk estimates for worst case; low to medium confidence in dermal exposure estimates and medium confidence in inhalation exposure estimates; Assumes resident applies 1 gallon or 1 quart of diluted product in a day
(12) Ornamental Application (Short-term) (Dursban 1-12 Insecticide, EPA Reg. 62719-56)						
Residential Mixer/Loader/ Applicator Low pressure Handwand	SS, SP, no gloves	Residential SOPs (minimum : 1 oz/3gal H20)	270	18,000	270	Central-tendency to high-end risk estimates; low and medium confidence in the dermal and inhalation exposure estimates, respectively. Assumes resident applies 5 gallons of diluted product/day.
		Residential SOPs (typical 4 oz/3 gal H20)	70	4,700	69	
		Residential SOPs (max. 1 qt/3 gal H2O)	8	560	8	
Residential Mixer/Loader/ Applicator Hose End Sprayer	SS, SP, no gloves	Residential SOPs (minimum : 1 oz/3gal H20)	900	57,000	880	Central-tendency to high-end risk estimates; low confidence in the dermal and inhalation exposure estimates. Assumes resident applies 5 gallons of diluted product/day.
		Residential SOPs (typical 4 oz/3 gal H20)	230	15,000	230	
		Residential SOPs (max. 1 qt/3 gal H2O)	28	1,800	28	
(13) Mosquitocide Mixer/Loader/Applicator (PHED V1.1) (Short- and intermediate-term) (Mosquitomist One EPA Reg. 8329-24)						
Mixer/Loader--Aerial	PPE double layer clothes and gloves	PHED V1.1	120 (ST) 24 (IT)	34 (ST&IT)	26 (ST) 14 (IT)	High end risk estimates. Application rate of 0.023 lb ai/acre for 7500 acres
	Engineering Controls (enclosed cockpit) single layer clothes and gloves		236 (ST) 47 (IT)	490 (ST&IT)	160 (ST) 43 (IT)	

Table 10. Estimates of Risks to Commercial Applicators and Residents Applying Chlorpyrifos in the Residential/Recreational Environment

Application Scenario	Clothing	Method of Evaluation	MOE			Risk Characterization/ Uncertainties
			Dermal	Inhalation	Total	
Mixer/Loader--Ground-based fogger	PPE, single layer clothes and gloves		1010 (ST) 200 (IT)	390 (ST&IT)	280 (ST) 133 (IT)	High end risk estimates. Application rates of 0.005 and 0.01 lb ai//acre for 3000 acres. Surrogate ground-based fogger exposure data are not available, and therefore, it was necessary to extrapolate from airblast exposure data
	engineering controls (enclosed cab) and single layer clothes and gloves		270 (IT)	2800 (IT)	250 (IT)	
Aerial Applicator	engineering controls (enclosed cockpit) and single layer clothes and no gloves		400 (ST) 81 (IT)	600 (ST&IT)	240 (ST) 71 (IT)	High end risk estimates. Application rate of 0.023/acre for 7500 acres
Ground-based fogger Applicator	engineering controls (enclosed cab) and single layer clothes and no gloves		610-1230 (ST)	520-1040 (ST)	280-560 (ST)	High end risk estimates. Application rates of 0.005 and 0.01 lb ai/acre for 3000 acres. Surrogate ground-based fogger exposure data are not available, and therefore, it was necessary to extrapolate from airblast exposure data
			120-250 (IT)	520-1040 (IT)	100-200 (IT)	

LS=Long sleeves; LP = Long pants; SS = short sleeves; SP = short pants
H20 = water; ST = short-term (1- 30 days); IT = intermediate term (30 days to 6 months) LT = long term (> 6 months)
NE = Not evaluated

TABLE 11 Crop Grouping Matrix by Potential for Dermal Contact			
Potential for Dermal Contact	**Transfer Coefficient (cm^2/hr)**	**Activities**	**Crops**
Low	2,500	Harvest	Alfalfa, asparagus, small grains (wheat, sorghum, milo), soybeans, cole crops, mint
		Sort/Pack	Sugar beets, radishes, rutabagas
Medium	4,000	Harvest, stake/tie, scout, irrigate	Cranberries, strawberries
		Irrigate	Christmas trees
		Late season scouting	Cotton
High	10,000	Harvest	Sunflowers, sugar beets, corn (up to 1.5 lb ai/A as a foliar treatment), sweet potatoes, radishes, rutabagas, turfgrass (sodfarm) for fire ants, almond harvesting
		Cut/harvest, prune, transplant, ball/burlap	Christmas trees

TABLE 12 Restricted Entry Intervals (REIs) for Chlorpyrifos: General				
Potential for Dermal Contact	**Short-Term REIs (days)**		**Intermediate-Term REIs (days)**	
	1 lb ai/A	**2 lb ai/A**	**1 lb ai/A**	**2 lb ai/A**
LOW	1	1	1	1
MEDIUM	1	No Crops	1	No Crops
HIGH	1	1	1	2
Scouting (Various Crops)	0	1	1	1

TABLE 13
Restricted Entry Intervals (REIs) for Chlorpyrifos:
Cauliflower, Citrus and Tree Nuts & Fruit

Activity	Short-Term REIs (days)					Intermediate-Term REIs (days)				
	Almonds	Apples	Pecans	Cauli-flower	Citrus	Almonds	Apples	Pecans	Cauli-flower	Citrus
Scouts	2	1	0	1 to 3	2	2	1	0	1 to 3	2
Harvesting	5	3	1	5 to 8	5	7	4	2	7 to 10	5
Pruning (wet cond.)	NE	NE	NE	NA	4	NE	NE	NE	NA	5
Pruning (dry cond.)	NE	NE	NE	NA	2	NE	NE	NE	NA	2

NE = Not Evaluated

Table 14
Chlorpyrifos Surrogate Occupational Postapplication Assessment for Golf Course Turf Treatment

Crop	Application Rate	DAT (a)	TTR from WP (Fg/cm^2) (b)	Mow/Maintain Transfer coefficient =500 cm^2/hr		Mow/Maintain Transfer coefficient =1,000 cm^2/hr	
				Potential Dermal Dose (mg/kg/day) (c)	Short-term MOE (d)	Potential Dermal Dose (mg/kg/day) (c)	Short-term MOE (d)
Golf Course Turf	4.0	0	0.414	0.024	210	0.047	110

(a) DAT is "days after treatment."
(b) Turf Transferable residues (TTR) from MRID 448296-01 based on average of CA, IN and MS sites following application of 4 lb ai/ Acre of Dursban 50W.
(g) Dermal Dose = TTR (Fg/cm^2) x Transfer coefficient (cm^2/hr) x conversion factor (1 mg/1,000) x 8 hr/day duration x dermal absorption x 1/70 kg body weight. The target MOE of 100 is based on 10x interspecies and 10x intraspecies.
(d) Short-term MOE = NOAEL of 5 mg/kg/day / Potential dermal dose (mg/kg/day).

Table 15. Estimates of Post-Application Risks to Residents/Recreational Users				
Reentry Scenario	**Method of Evaluation**	**Central-tendency MOE**		**Risk Characterization/ Uncertainties**
		Adult	**Child**	
(1) Crack & Crevice Treatment of Kitchen and Bathroom (0.5% Dursban Pro diluted spray, EPA Reg. 62719-166) (Short and Intermediate Term)				
Maximum 1-Day Inhalation Exposure:	Biomonitoring Study, with environmental measurements	560	130	Central-tendency to High-end risk estimates; assumes exposure exclusively through inhalation and that children spend 21 hours/day (50th percentile for 1-4 yr old at home) in a treated room (i.e., home, schools, day care centers, etc). This could over-or under-estimate risk because it is compared to a 90 day inhalation NOAEL for rats exposed 6 hours/day.
10-Day TWA Inhalation Exposure		670	360	
(2) Crack & Crevice Treatment Using Residential SOPs (0.5% Dursban Pro diluted spray, EPA Reg. 62719-166) (Short-term)				
Dermal Exposure From Carpets	Highest deposition from untreated family room in biomonitoring study (room adjacent to treatment) and Residential SOPs	1950	1360	Low-end risk estimates; highest deposition from untreated room used in conjunction with updated SOP assumptions (i.e., 5% of residues are dislodgeable, 50% extracted in saliva, transfer coefficients of 6,000 and 16,700 cm^2 for children and adults, respectively). Inadequate deposition data collected in treated rooms in registrant study.
Dermal Exposure From Surfaces		3900	2700	
Oral Exposure		NE	4100	
Total Crack &Crevice (Sum of 1 and 2) Inhalation, Dermal and Oral		390 (1 day) 440 (10day)	110 (1 day) 240 (10day)	Central-tendency risk estimates. Inhalation estimates are central-tendency to high end, but dermal and oral exposure estimates are low end.
(3) Pet Collar Uses (11 month efficiency) (Long-term)				
Dog Collar (EPA No. 45087-49; 3.44 g ai); Cat Collar (EPA No. 4306-16; 0.93 g chlorpyrifos)				
Total Exposure	Residential SOPs	670 (dog) 2500 (cat)	140 (dog) 530 (cat)	Central-tendency to high-end risk estimates; assume that a total of 1% ai is available from collar over 11 months only from dermal exposure. Assumes incidental ingestion and inhalation are negligible. Based on preliminary data, equivalent to approximately 2 , 3 or 105 min per day of vigorous dermal contact with collar, neck fur or back fur over 11 months.

Table 15. Estimates of Post-Application Risks to Residents/Recreational Users				
Reentry Scenario	Method of Evaluation	Central-tendency MOE		Risk Characterization/ Uncertainties
		Adult	Child	
(4) Termiticide Treatment Includes Risk Mitigation (adjustment to 0.5% ai as Dursban TC) (Intermediate and Long-term) (See Table A-1, Appendix A)				
Basement Construction				
90-Day Incremental Time-weighted- average (TWA)	Registrant study that collected air measurements in 7 homes from 7 days to 1 year post-treatment.	13,000 (2,100-30,000)	3800 (600-8700)	Median MOE with range of MOEs presented in parentheses. Values adjusted from 1% ai (typical rate) to 0.5% ai (minimum rate). Assumes a child spend 20 hours in a treated residence.
1-Year Incremental TWA		3,800 (930-8,800)	1,100 (270-2,500)	
Crawl-Space-type Construction				
90-Day Incremental Time-weighted- average (TWA)	See comments under basement construction.	7,300 (3,300-25,000)	2,100 (950-7,200)	See comments under basement construction.
1-Year Incremental TWA		1,800 (1,200-7,400)	530 (340-2,100)	
Slab Type Construction				
90-Day Incremental Time-weighted- average (TWA)	See comments under basement construction.	6,600 (1,500-20,000)	1,900 (440-5,800)	See comments under basement construction.
1-Year Incremental TWA		2,100 (960-7,600)	600 (280-2,200)	
Plenum-Type Construction				
90-Day Incremental Time-weighted- average (TWA)	See comments under basement construction.	6,600 (1,600 - 22,000)	1,900 (460 - 6,400)	See comments under basement construction. 1-Year incremental TWA based on five houses, due to insufficient sampling for two houses. Sampling not conducted beyond days 30 and 7 for houses P-6 and P-7, respectively. Based on available data, these houses had higher air concentrations than the other houses.
1-Year Incremental TWA		2,600 (940-9,500)	760 (270-2,700)	

Table 15. Estimates of Post-Application Risks to Residents/Recreational Users				
Reentry Scenario	Method of Evaluation	Central-tendency MOE		Risk Characterization/ Uncertainties
		Adult	Child	
(5) Insecticidal Dust Products (Insufficient data to evaluate; see text)				
Broadcast Turf Application (Residential/Recreational) (Short-term)				
(6) Chlorpyrifos Spray (Dursban Turf Insecticide)				
Inhalation	Biomonitoring Study, with environmental measurements. Application of 0.29% chlorpyrifos spray at 4 lb ai/acre	170	20	Average represents central-tendency risk estimates based on arithmetic mean exposure from biomonitoring study in adults, where chlorpyrifos applied at the maximum label rate of 4 lb ai/acre. Based on 2 hour dermal contact with lawn the day of treatment. Maximum represents the highest exposed individual in the study. Study does not adequately address frequent hand to mouth activity of children, or incidental ingestion of soil or residues on treated grass by children. Application at typical rate of 1 lb ai/acre would potentially result in lower exposures (see below).
Dermal		10	12	
Oral		NE	400	
Total Absorbed Dose		Average: 9 -24 Maximum: 5.6-15	Average: 7.5-15 Maximum: 6-12	
Total Absorbed Dose	Biomonitoring Study with adjustment for 1 lb ai/acre	Average: 36-96	Average: 30-60	Low to Central-tendency risk estimates, based on typical application rate of 1 lb ai/acre.
(7) Granular Formulation of 0.5% Chlorpyrifos (Dursban Insecticide) (1.8 lb ai/acre)				
Inhalation	Biomonitoring Study, with environmental measurements	330	400	Average represents central-tendency risk estimates based on arithmetic mean exposure from biomonitoring study in adults. Based on 2 hour dermal contact with lawn the day of treatment; does not adequately address frequent hand to mouth activity of children, or incidental ingestion of soil or granules by children. Maximum MOE is for the highest exposed individual in the study.
Dermal		190	90	
Oral		NE	6000	
Total Absorbed Dose		Average: 110-120 Maximum: 42-45	Average: 73-75 Maximum: 29	
(8) Golf Course Treatment (Dursban Turf Insecticide; EPA Reg 62719-35) (1-4 lb ai/acre) (Short-term)				
Adolescent Golfer (12 yrs; 44kg)	Residential SOPs and surrogate residue data from flurprimidol study the day of treatment	360 (4 lb ai/acre) 1500 (1 lb ai/acre)		High-end risk estimates. Assumes exclusively dermal exposure the day of turf treatment Assumes a 4 hour exposure for a 18 hole round of golf.

Table 15. Estimates of Post-Application Risks to Residents/Recreational Users				
Reentry Scenario	Method of Evaluation	Central-tendency MOE		Risk Characterization/ Uncertainties
		Adult	Child	
Adult Golfer		600 (4 lb ai/acre) 2400 (1 lb ai/acre)		

Table 15. Estimates of Post-Application Risks to Residents/Recreational Users				
Reentry Scenario	Method of Evaluation	Central-tendency MOE		Risk Characterization/ Uncertainties
		Adult	Child	
(9) Aerial and Ground-Based Fogger Mosquitocide Application (Mosquitomist One, EPA Reg. 8329-24) (0.01 lb ai/acre) (Short-term)				
Dermal	Literature studies, the AgDrift Model and the updated Residential SOPs	42,000	26,000	High-end risk estimates based on the updated Residential SOPs. Assumes long-term inhalation exposure is negligible based on low application rate and infinite dilution.
Oral (hand to mouth)		NE	13,000	
Oral (Turfgrass Ingestion)		NE	54,000	
Oral (Soil Ingestion)		NE	20,000,000	
Total Exposure		42,000	15,000	
(10) Yard and Ornamental Sprays (Evaluated based on analogy to Lawn Products; see text)				
(11) Perimeter Treatment of Residence (Dursban Pro, EPA Reg. 62719-166) (4.35 lb ai/acre) (Short-term)				
Dermal	Updated Residential SOPs Residential	NE	8 minutes of play is equivalent to a MOE of 1000	High-end risk estimates based on the updated Residential SOPs. Assumes a child plays on treated turf the day of treatment. The most critical items are the probability that a child would play within 6 to 10 feet of a residence and for what duration a child would be in the treatment zone.
Oral (hand to mouth)		NE	7 hand to mouth events is equivalent to a MOE of 1000	
Oral (Soil Ingestion)		NE	MOE = 2300	

4.4.4.4 Incident Reports

Chlorpyrifos is one of the most widely used insecticides in the home both by consumers and PCOs or exterminators. In a 1990 EPA-sponsored survey of pesticide use in households, chlorpyrifos was the fourth most commonly used insecticide, present in 18% of all households. A 1993 EPA survey of PCOs found it was the number one insecticide in use and accounted for a quarter of the poundage used in residential settings. Consequently, there have been many reports of human exposure and poisonings due to the widespread use of chlorpyrifos. The human poisoning incidents associated with chlorpyrifos exposure have been evaluated and summarized in the attached memorandum from J. Blondell to D. Smegal, April 20, 2000. HED notes that approximately 98% of chlorpyrifos exposures discussed below are due to products removed under the risk mitigation plan.

Data from the Nation's Poison Control Centers in 1996 reported approximately 116,000 unintentional exposures to all pesticides, of which, 16% were due to organophosphate (OP) pesticides, and 5,188 or 4.5% were attributed to chlorpyrifos. These numbers are based on exposures to single products, a small proportion of which may contain additional active ingredients besides chlorpyrifos. Given that 30% of the organophosphate poisonings were not specifically identified by active ingredient, the actual number of chlorpyrifos cases is probably close to 7,000 or 6% of all pesticide-related exposures. Many of these exposures involve small children who were exposed but never developed symptoms. In 1996 there were 1,109 symptomatic cases related to chlorpyrifos that were judged to have effects related to the exposure, although most (83%) had only minor symptoms (e.g., headache, nausea, vomiting, dizziness and diarrhea) that could be treated at home. From 1993 through 1996, there were an average of 116 unintentional chlorpyrifos cases per year with moderate to severe outcomes (including one fatality) reported in residential settings.

The possibility of risk from chlorpyrifos exposure is very similar to the other OP pesticides (e.g., diazinon, malathion, dichlorvos) that have significant residential uses for both children and adults. The one exception is the percent of cases with fatal or life-threatening outcome (not including suicide attempts), where chlorpyrifos had the highest percentage (0.46% based on 18 cases) of any of the other 13 OP pesticides, that was 50% higher than any of the non-OP pesticides. Between 1993 and 1996, there was one fatality and 34 life-threatening cases attributed to chlorpyrifos exposure. The fatality was a 22 month old boy who accidently ingested chlorpyrifos that had

been placed in a cup. Measures called for in the 1997 Chlorpyrifos Risk Reduction Plan, in part, were aimed a preventing such poisoning incidents.

Chlorpyrifos ranked third of the 13 OPs for serious outcomes resulting from exposure to environmental residues left after application or use. Environmental residues accounted for 15% of the chlorpyrifos exposures and 30% of the cases with serious outcomes (moderate or life-threatening), which was double the incidence for non-OP pesticides.

A particular concern with chlorpyrifos are reports of exposures and poisonings related to use by PCOs. A review of the Poison Control Center data for four years (1993-1996) found over 1000 reports of exposure (250 per year) to chlorpyrifos products that would most commonly be used by PCOs in residential settings. A total of 325 of these cases were symptomatic, 241 cases were seen in a health care facility, 35 were hospitalized and 16 were admitted to an intensive care unit (ICU). Chlorpyrifos PCO products accounted for 9% of the exposures, but 21-24% of the life-threatening/fatal cases, hospitalized cases and cases seen in an ICU. Note that the number of cases involving PCO products is relatively small compared to the exposure and symptomatic cases involving consumer products. Just 4% of the product identified chlorpyrifos exposures in children under age six involved PCO products, and for adults and children over age six the figure was 15%. Also, some of the more serious cases, both for PCO and homeowner products, were due to broadcast carpet treatment, fogger and pet uses that were voluntarily canceled in 1997.

Another source of concern with all the OP pesticides, including chlorpyrifos, are the frequent anecdotal reports of chronic neurobehavioral effects and multiple chemical sensitivity. Kilburn (1999) documented neurobehavioral effects (including signs consistent with peripheral neuropathy in 11 cases) among 22 patients reporting exposure to chlorpyrifos, 10 of which were self-referred and 12 referred by attorneys. In addition to these reports, there were 14 self-reported but unconfirmed cases (without medical documentation) of chronic neurobehavioral effects submitted by Dow AgroSciences during 1998-1999. Another 73 cases were reported to EPA during the public comment period (October-December 1999) for chlorpyrifos. A few of these cases may have overlapped the reports from Kilburn and Dow AgroSciences. Twelve of the 73 cases provided some, often very limited, medical documentation of their effects. Out of all of the cases reported by Kilburn, Dow AgroSciences or directly to EPA there were only about 3-4 with laboratory confirmation (e.g., reduced cholinesterase) of their

exposures. Neurobehavioral effects reported include persistent headaches, blurred vision, muscle weakness, fatigue, and problems with mental function including memory, concentration, depression, and irritability.

HED suspects that these chronic neurobehavioral effects are caused by the acute poisoning, partly from a case-control study in California partly from case-control (cross sectional) studies of other OP pesticides similar to chlorpyrifos, and most recently from a NIOSH study. With EPA support, NIOSH completed a study of 191 current and former PCOs that apply chlorpyrifos as a termiticide in North Carolina. An extensive battery of neurological and neurobehavioral tests was administered. The study (Steenland et al. 2000), concluded "this cross-sectional study of workers exposed to chlorpyrifos . . . found few exposure related effects for most tests, including a clinical exam. However, the exposed did not perform as well as the non-exposed on pegboard turning tests and some postural sway tests. Furthermore, exposed subjects reported more symptoms than non-exposed subjects; this is a cause for concern because previous studies lend some support to this finding." Among acutely poisoned subjects the study stated, "Eight men who reported past chlorpyrifos poisoning had a pattern of low performance on a number of tests, which is consistent with prior reports of chronic effects of organophosphate poisoning." Finally, the study noted the following reservation, partly due to the relatively heavy exposure experienced by study participants, "Although this was a relatively large study based on a well-defined target population, the workers we studied may not be representative of all exposed workers and caution should be exercised in generalizing our results." (Steenland et al. 2000). These findings are consistent with an earlier review that suggested chlorpyrifos may be a cause of chronic neurobehavioral effects in some subsets of sensitive people who have been poisoned (Blondell and Dobozy 1997). In addition to the studies described above, DAS has agreed to undertake an epidemiologic study of manufacturing workers.

As noted previously, four uses of chlorpyrifos have been voluntarily canceled and removed from the market: paint additives; shampoos, sprays and dips used on pets; indoor broadcast flea control products; and household foggers. Poison Control Center data for 1993-1996 suggest that as many as 20-25% of symptomatic exposures in residential settings were related to these uses. All of these residential uses involve either concentrates or widespread applications that involve greater potential for exposure to consumers than do other forms and uses of chlorpyrifos. Therefore, substantially less exposures and hazards are expected when additional years of

poisoning surveillance data become available. DAS is continuing its' efforts to monitor poisoning incidents through its agreement with a Poison Control Center that takes telephone contacts from the public and the health care community concerning chlorpyrifos. Follow up information to determine the circumstances that lead to exposure and poisoning should be useful.

4.4.5 Pet Incident Reports

A review and analysis of the poisoning incident reports on domestic animals for chlorpyrifos was conducted in 1995 (attached memo from V. Dobozy to B. Kitchens, January 23, 1995) and was updated in 1999 (attached memo from V. Dobozy to D. Smegal, April 26, 1999, D255514). In the 1995 analysis, poisoning incidents in dogs and cats were categorized as exposure by direct applications (flea and tick dips, sprays, collars, etc) or by premise applications (household and lawn treatments). The analysis found that the majority of the incidents in domestic animals involved cats, although the chemical is registered only for use in flea collars for this species. Cats that were exposed to products registered only for use on dogs, mainly dips, experienced a high incidence of death (30%). There was also evidence of misuse of treatment products, including practices such as applying these products directly to animals and not removing pets from premises during applications.

In 1996, PR Notice 96-6 was finalized, which requires the revision of labels for all products administered directly to animals to ensure adequate directions for use and warning information. In 1997, the registrant voluntarily agreed to cancel chlorpyrifos registrations for indoor broadcast flea control and direct application pet products (sprays, shampoos, and dips), except flea collars, to establish specific protection measures for pets during and immediately after application, and to expedite implementation of PR Notice 96-6 on pet products.

An evaluation of incident reports for domestic animals for the years 1996 through 1998 (memo from V. Dobozy to D. Smegal, April 26, 1999, D255514) revealed that there has been a decrease in the percentage of incidents resulting from exposure to products registered for direct use on animals, but an increase in the percentage of incidents resulting from premise exposure. In addition, deaths are still being reported, especially for cats. The cancellation of indoor broadcast flea control applications and products for direct application to dogs and cats should reduce the risk of serious adverse reactions and deaths, however time is required to eliminate all chlorpyrifos products from store shelves. Therefore, it may be premature to review the Incident Data System (IDS) for evidence that these actions were effective.

4.5 Chlorpyrifos Exposure Estimates in the U.S. Population

Because of chlorpyrifos' extensive use on food and in homes and the workplace, the majority of the U.S. population is exposed to this pesticide. Literature studies, in addition to several of the registrant-submitted biomonitoring studies, have estimated typical or baseline exposure to chlorpyrifos by measuring the urinary excretion of 3,5,6-TCP, the primary metabolite of chlorpyrifos. TCP has a biological half-life of approximately 27 hours, therefore, the urinary TCP levels reflect recent exposure. It should be noted however, that exposure to chlorpyrifos-methyl, 3,5,6-TCP (the animal, and plant metabolite and environmental degradate of chlorpyrifos and chlorpyrifos-methyl), and trichlorpyr (a herbicide) also contribute to an unknown degree to 3,5,6-TCP urinary concentrations, thus the chlorpyrifos exposure estimates presented in this section represent an upper-bound estimate. Chlorpyrifos contributes significantly more to urinary TCP than chlorpyrifos-methyl and trichlorpyr based on relative annual U.S. usage of approximately 21 to 24 million pounds of chlorpyrifos (of which approximately 11 million are used in residential and recreational settings) versus 92,000 pounds of chlorpyrifos-methyl and 700,000 pounds of trichlorpyr.

HED has conducted a preliminary risk assessment for TCP, which is in the attached memorandum from S. Knizner to D. Smegal, D265035 June 5, 2000.

Table 16 summarizes the typical upper-bound baseline exposure to chlorpyrifos estimated from the registrant submitted biomonitoring studies of TCP measurements, and the scientific literature. These values represent worst case estimates because all of the TCP was attributed to chlorpyrifos.

Registrant Residential Biomonitoring Studies

DAS recently conducted four biomonitoring studies to quantify exposures to residential populations following the use of chlorpyrifos products in the home. Volunteers were typically adults of both sexes between the ages of 25 and 65. Other details were not provided (i.e., ethnicity). For all of these studies, baseline chlorpyrifos exposures of the volunteers were quantified by analysis of urinary 3,5,6-TCP prior to commencement of the study. Quantification of baseline chlorpyrifos exposure for each volunteer was necessary in order to determine actual exposure associated with a product's use. For each of these studies, baseline TCP measurements were subtracted from total TCP measurements to quantify chlorpyrifos exposure in the biomonitoring study. In addition, residents were instructed to avoid chlorpyrifos exposure for several days (typically one week to 10 days) prior to the measurement of baseline levels. Therefore, the baseline exposures are most likely attributed to dietary exposure of chlorpyrifos, chlorpyrifos-methyl and TCP.

In August 1999, DAS submitted a TCP Biomonitoring study that assesses children's potential household exposure to chlorpyrifos and its environmental degradate, TCP (MRID 44889501). The study evaluated urinary TCP concentrations of 416 children 0-6 years of age in North and South Carolina; 120 children were from households treated with a termiticide containing chlorpyrifos, and 296 children were from households identified from the general population sample. TCP was detected in 100% of the children's urine. The 24 hour TCP excretion ranged from 0.09 to 75.79 Fg TCP/g creatinine/kg body weight, with a mean value of 1.19 Fg TCP/g creatinine/kg body weight. These values correlate to approximately 0.045 to 38 Fg chlorpyrifos /kg/day, with a mean value of 0.6 Fg/kg/day. It should be noted that 73% (303/413) and 11% (47/413) of the children in this survey lived in homes that had been treated with a chlorpyrifos-containing insecticide indoors or with a termiticide, respectively within the past year. In addition, 64% of the children (264/412) also were from homes that had a lawn treatment within the past year. HED is currently reviewing this study.

Scientific Literature

The study published by Hill et al. (1995) measured the biomarker 3,5,6-TCP in 993 adults (20-59 years old) participating in the National Health and Nutrition Examination Survey III, known as NHANES III from 1988 - 1994. The individuals were selected from a broad spectrum of the U.S. population reflecting both sexes and different age groups, races/ethnicities, urban/rural residences and regions of the country. 3,5,6-TCP was detected in 82% of the individuals evaluated. The average TCP concentration was 4.5 Fg/L or 3.1 Fg TCP/g creatinine. The results of NHANES III differ significantly from the NHANES II survey collected between 1976 and 1980, where only 5.8% of the 6990 people evaluated had concentrations of 3,5,6-TCP greater than the detection limit of 5 Fg/L. In the NHANES III survey, 31% of the 993 people had 3,5,6-TCP concentrations greater than 5 Fg/L. It should be noted however, that the lower detection limit of 1 Fg/L in the NHANES III study could partially account for the increased frequency of detection of 82%. The results of this study are presented below in Table 14. It is possible that the registration of chlorpyrifos-methyl for use on stored grains in 1985 contributes to the increased frequency and concentration of TCP measurements between the NHANES II and III results. In addition, chlorpyrifos-methyl was detected at greater frequencies than chlorpyrifos in the 1991-1997 Total Diet Study (FDA 1999). In this study,100% of samples for several commodities containing flour (i.e., whole wheat bread, tortilla flour, rye bread, cracked wheat bread, english muffin, teething biscuits, pretzels, fish sticks, white roll, and butter type crackers) contained measurable chlorpyrifos-methyl residues.

A recent study of 65 recently-exposed termiticide applicators (Steenland et al. 2000) reported an average urinary TCP level of 629.5 Fg/L, compared to the 4.5 Fg/L for the general U.S. population from Hill et al. (1995).

The Minnesota Children's Pesticide Exposure Study, which is one of the National Human Exposure Assessment Surveys (NHEXAS), evaluated 102 children ages 3-12 (mean 7.6 ± 2.9 yrs), stratified by those with more frequent residential insecticide usage (personal communication with James Quackenboss, March 1, 1999). This study was initiated to assess children's actual exposures to pesticides. The study examined the relationship between environmental concentrations and urinary biomarker levels of 3,5,6-TCP from a population-based study of total exposure in urban and non-urban children. Tap water, personal, indoor, and outdoor air, house dust, and soil were monitored over 6 days while food and beverage monitoring was conducted over 4 days. Urine samples were obtained for 87% (89) of the study subjects. Preliminary data were presented at the International Society for Environmental Epidemiology (ISEA) conference in Boston in August 1998 (Adgate et al. 1998), where 92% of the 89 children had measurable levels of 3,5,6-TCP in their urine. It should be noted, however, that the study over sampled homes that frequently used pesticides, and 30% of the households had used chlorpyrifos. The results from the metabolite analysis suggest that these children have higher concentrations of 3,5,6-TCP than was reported for the NHANES-III adult population (medians of 8 and 2 Fg/L TCP, respectively) (Quackenboss et al. 1998). The final study results are anticipated to be available in 2000.

Macintosh et al. (1999) evaluated urinary TCP levels in 80 individuals in Maryland during 1995-1996. Up to six samples were collected from each individual over a period of a year. TCP was detected in 96% of the 346 samples at a median concentration of 5.3 Fg/L and 4.6 Fg/g creatinine. The geometric mean concentrations of TCP were significantly greater in samples collected during the spring and summer of 1996 than in the preceding fall and winter. In addition, the geometric mean TCP concentrations differed significantly between Caucasian (GM = 5.7 Fg/g creatinine) and African-American (GM = 4 Fg/ g creatinine) participants and among education levels but were not significantly different among groups classified by gender, age, or household income. The mean and median TCP concentrations in this study (5.8 and 4.6 Fg/g creatinine) are approximately twofold greater than those measured in the NHANES III (3.1 and 2.2 Fg/g creatinine, respectively) (Hill et al. 1995), however the upper end of the distributions are approximately equal. Individual urinary TCP levels varied over time and were highly variable, indicating that a single measure of urinary TCP levels is not sufficient to adequately characterize the relative magnitude of a person's typical exposure to chlorpyrifos.

Buckley et al. (1997) evaluated 18 nonsmoking adults from nine homes in the Lower Rio Grande Valley (LRGV) in Texas during the spring and summer 1993. Urinary TCP was significantly higher in the summer relative to the spring, and was correlated with air and dust concentrations. TCP was detected in 77% (13/17) and 92% (11/12) of the spring and summer samples, respectively at median concentrations of 1.9 and 3.2 Fg/L, respectively.

Table 16 summarizes the typical upper-bound baseline exposure to chlorpyrifos estimated from the Hill et al. (1995) and DAS biomonitoring studies of TCP measurements. These values represent worst case estimates because all of the TCP was attributed to chlorpyrifos. All exposure estimates have been normalized for creatinine excretion. The assumptions and equations are presented in the footnotes.

Table 16
Upper Bound Chlorpyrifos Exposure Estimates Based on Biomonitoring of Urinary TCP

Source/Study	Sample Size	Percent with TCP in urine	Mean Chlorpyrifos Dose Fg/kg/day	95th Percentile Fg/kg/day	Range of Chlorpyrifos Dose Fg/kg/day
Residential Biomonitoring Studies					
Child TCP Biomonitoring study (0-6 yrs old, North and South Carolina, 1998) (a)	416	100%	0.6	1.32	0.045-4.7
Residential exposures from Lawn treated with Chlorpyrifos Spray (MRID 43013501) (Adults) (b)	8	100%	0.3	NE	0.09 - 0.6
Residential Exposures from Lawn treated with Granular Chlorpyrifos (MRID 44167101) (Adults) (b)	9	100%	0.5	NE	0.21 - 1.47
Residential Exposure from Crack and Crevice Application (MRID 44458201) (Adults) (b)	6	100%	0.4	NE	0.1-0.86
Residential Exposures from Application of a Ready-to-Use Formulated Product (MRID 44739301) (Adults) (b)	15	100%	0.12	NE	0.05-0.3
Literature Studies					
Hill et al. 1995 (NHANES III) (Adults, 1988-1994) (c)	993	82%	0.2 (b)	0.52	ND - 2
MacIntosh et al. 1999 (Adults, Maryland, 1995-1996) (d)	80 people (329 samples)	96%	0.37	1	0.013-2.2
Buckley et al. (1997) (Adults, Texas, 1993) (e)	18	Spring: 77% Summer: 92%			

ND = not detected

NE = not estimated

(a) Creatinine adjusted concentrations for 24 hour TCP excretion ranged from 0.09 to 15.8 Fg TCP/g creatinine/kg body weight, with a mean value of 1.19 Fg TCP/g creatinine/kg. In the initial study, the highest child was 75.79 Fg TCP/g creatinine/kg, which is equal to approximately 38 Fg/kg/day chlorpyrifos. A more recent submission, March 2000, reported lower levels of TCP in this child of 15.8 Fg TCP/g creatinine/kg, which is equivalent to approximately 4.7 Fg/kg/day chlorpyrifos. The 95th percentile was 2.63 Fg TCP/g creatinine/kg. Assumes child specific body weight, and average creatinine excretion of 0.2 g/day from 416 children. Assumes steady-state between exposure and excretion.

(b) Based on pre-study 3,5,6-TCP results in urine. See HED study reviews for details

(c) Creatinine adjusted concentrations of mean 3.1 and maximum of 34 Fg TCP/g creatinine, respectively that assumes an average creatinine excretion rate of 1.8 g/day (Tietz 1982), a body weight of 70 kg, and that 72% of chlorpyrifos is excreted in the urine. A molecular weight adjustment was also made 350.6 chlorpyrifos/ 198 TCP. Assumes steady-state between exposure and excretion. Example calculation: Dose (Fg/kg/day) = [(3.1 Fg TCP/g creatinine * 350.6/198 * 1.8 g/day) / (70 kg * 0.72 (fraction chlorpyrifos excreted as TCP)].

(d) creatinine adjusted concentrations of <0.2, 5.8, 16 and 35 Fg TCP/g creatinine for minimum, mean, 95th percentile and maximum, respectively. Assumes an average creatinine excretion rate of 1.8 g/day (Tietz 1982), a body weight of 70 kg, and that 72% of chlorpyrifos is excreted in the urine. A molecular weight adjustment was also made 350.6 chlorpyrifos/ 198 TCP. Example calculation: Dose (Fg/kg/day) = [(35 Fg TCP/g creatinine * 350.6/198 * 1.8 g/day) / (70 kg * 0.72 (fraction chlorpyrifos excreted as TCP)].

(e) Creatinine adjusted concentrations not presented. Median TCP concentrations of 1.9 and 3.2 Fg/L and maximum concentrations of 6.4 and 11 Fg/L for spring and summer, respectively.

5.0 Aggregate Risk Assessments and Risk Characterization

The Food Quality Protection Act amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA, Section 408(b)(2)(A)(ii)) require that for establishing a pesticide tolerance "that there is reasonable certainty that no harm will result from aggregate exposure to pesticide chemical residue, including all anticipated dietary exposures and other exposures for which there are reliable information." Aggregate exposure is the total exposure to a single chemical (or its residues) that may occur from dietary (i.e., food, and drinking water), residential and other non-occupational sources, and from all known or plausible exposure routes (oral, dermal and inhalation). Aggregate risk assessments are typically conducted for acute (1 day), short-term (1-30 days), intermediate-term (30 days to several months), and chronic (several months to lifetime) exposure.

DAS has submitted a probabilistic Integrated Exposure Assessment (MRID No. 44104001, September 1996). This submission is in internal HED review, because the Agency policy on aggregate probabilistic risk assessment is still in development. This submission, however, has been used by the Agency in developing policy and will be evaluated once this policy is finalized and has undergone peer review.

The total residential MOEs (dermal, inhalation, and inadvertent oral exposures) for all the residential post-application exposure scenarios, except mosquitocide use, and golf course use alone exceed HED's level of concern. In addition the acute dietary exposure and risk estimates exceed HED's level of concern. However, HED conducted acute, short-term and chronic aggregate assessments assuming the mitigation plan is adopted. As noted previously, the mitigation plan would reduce potential chlorpyrifos exposures on apples, grapes and tomatoes, and mitigate the residential/recreational exposures.

5.1 Acute Aggregate Risk

The acute aggregate risk estimate to chlorpyrifos addresses exposures from food and drinking water. For the highly refined acute probabilistic dietary exposure analysis, PDP, FDA and NFS monitoring data were used to the greatest extent possible, along with field trial data, and cooking and processing factors to assess dietary exposures. This aggregate assessment incorporates the mitigation plan (i.e., reduction of apple tolerance to 0.01 ppm based on dormant application, reduction of grape tolerance to 0.01 ppm based on domestic use pattern and deletion of the use on tomatoes).

With the mitigation measures, the chlorpyrifos acute dietary risk estimates range from 4.1% to 82% of the aPAD, with children (1-6 yrs) being the highest exposed population subgroup. Thus, the mitigated acute dietary (food) risk estimate associated with chlorpyrifos exposure is below the Agency's level of concern. Using conservative screening-level models, the acute estimated concentrations (EECs) of chlorpyrifos in groundwater (SCI-GROW) range from 0.007 to 0.103 Fg/L. The acute surface water EECs, based on upper-bound

monitoring data results, are 0.026 to 0.4 Fg/L, respectively. As shown previously on Table 7, and on Table 17 below, the EECs are less than the DWLOCs for all populations (highest EEC of 0.4 Fg/L is less than the lowest DWLOC of 0.9 Fg/L), indicating that acute food and drinking water exposures (except possible well contamination) do not exceed HED's level of concern. It should be noted that neither the SCI-GROW model nor the monitoring data reflect concentrations after dilution (from source to treatment to tap) or drinking water treatment. HED concludes that **acute aggregate chlorpyrifos exposure in food and water does not exceed HED's level of concern.**

Table 17
Summary of Acute Aggregate Exposure
Includes Risk Mitigation

Population Subgroup (a)	Acute PAD (Fg/kg/day)	Food Exposure 99.9th (Fg/kg/day) (b)	Max. Water Exposure (Fg/kg/day) (c)	Surface Water (Monitoring Data) (Fg/L)	Ground Water SCI-GROW, (excluding well contamination) (Fg/L)	Acute DWLOC (Fg/L) (d,e,f)
U.S. Population	5	0.237	4.76	0.026 to 0.4	0.007 to 0.103	166
All Infants (< 1 Year)	0.5	0.258	0.242			2.4
Children (1-6 years)	0.5	0.410	0.09			0.9
Females (13-50 years)	0.5	0.201	0.299			9

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.
(b) 99.9th percentile exposure. Values are from Table 3 (and rounded).
(c) Maximum Water Exposure (Fg/kg/day) = Acute PAD (Fg/kg/day) - [Acute Food Exposure (Fg/kg/day)].
(d) DWLOC (Fg/L) = Maximum water exposure (Fg/kg/day) x body wt (kg) ÷ water consumed daily (L/day)]
(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

Acute exposure to chlorpyrifos in groundwater as a result of well contamination from termiticide use could potentially result in exposures of concern. However, as noted previously, the groundwater exposures from well contamination resulting from termiticide use are highly localized. The implementation of PR 96-7 for termiticides has reduced the reported incidents of groundwater contamination resulting from termiticide treatments. For example, incidents associated with termiticide use were 28.2 per 100,000 homes in 1997 (pre PR-96-7), and were 8.3

per 100,000 homes in 1998 (post PR-96-7).

5.2 Short-Term Aggregate Risk

The short-term aggregate risk estimate includes chronic dietary (food and water) from chlorpyrifos uses, and short-term non-occupational exposures (i.e., residential/recreational uses). As noted previously, this aggregate assessment is based on the mitigation plan that would reduce potential chlorpyrifos exposures in food (apples, grapes and tomatoes) and in the residential/recreational environment. This assessment evaluates potential exposures resulting from continued chlorpyrifos use on golf courses at a reduced rate of 1 lb ai/acre (i.e., risks to golfers), in addition to potential exposures as a result of mosquito abatement activities.

Table 18 presents the aggregate exposure estimates for chlorpyrifos from diet and residential/non-occupational uses (golfing and mosquitocide abatement activities). Based on the mitigation plan, it was assumed that children (1-6 years) could be exposed to chlorpyrifos residues on turf as a result of ground-based fogger applications of a chlorpyrifos-containing mosquitocide, and through dietary exposures. Children 7-12 years were assumed to be dermally exposed to chlorpyrifos residues while playing golf (the day of treatment), and to ingest chlorpyrifos residues in the diet. Female residents were assumed to be concurrently exposed to chlorpyrifos via mosquito abatement activities (i.e., dermal contact with residues on turf), golfing (dermal contact turf residues the day of treatment), in addition through dietary exposures. The results of the exposure analysis for the individual scenarios are presented in detail in the Occupational /Residential Exposure Chapter for the RED for Chlorpyrifos (D266562, June 2000).

As shown on Table 18, aggregate MOEs are greater than 1000 for children 1-6 years, children 7-12 years and females 13-50 years, and therefore do not exceed HED's level of concern. Therefore, short-term DWLOCs were estimated to account for potential drinking water exposures.

Table 18
Summary of Aggregate Short-Term Exposure
Chronic Diet and Short-Term Residential Use
(Excludes Water)
Includes Risk Mitigation

Population Subgroup	Dietary Exposure with Risk Mitigation	Short-Term Residential/Recreational Exposure (Fg/kg/day)/ MOE Risk Mitigation			Total Aggregate MOE Estimate (b)
		Mosquitocide Postapplication		Golf Course Postapplication Exposure (1 lb ai/acre)	Diet and Residential/ Recreational Exposure
	Chronic Diet Exposure with FHE (Fg/kg BW/day) (a)/ MOE	Oral	Dermal	Dermal	Oral and Dermal
Children (1-6 years)	0.008 MOE = 62,500	0.013 MOE = 38,500	0.19 MOE = 26,000	NE	12,000
Children (7-12 years)	0.015 MOE = 33,000	NE	NE	3.4 MOE = 1,500	1,400
Females 13-50	0.006 MOE = 83,000	NE	0.14 (c) MOE= 36,000	2.45 (c) MOE = 2,000	1,900

NE = not evaluated.
FHE = Food Handling Establishment Use

(a) MOE calculated based on acute oral NOAEL of 500 Fg/kg/day, and short-term dermal NOAEL of 5000 Fg/kg/day for dermal exposures. No dermal absorption is necessary because dermal NOAEL is based on a dermal rat study.

(b) Oral and dermal exposures were combined because the oral and dermal endpoints are both based on plasma and RBC ChE inhibition.

(c) Adjusted from 70 kg to 60 kg for aggregate exposure.

The short-term DWLOC values are presented in Table 19. For each population subgroup listed, the acute PAD and the chronic dietary (food) exposure (from Table 4) for that subgroup were used to calculate the short-term DWLOC for the subgroup, using the formulas in footnotes of Table 19. The EECs are less than the DWLOCs for all populations (highest EEC of 0.1 Fg/L is less than the lowest DWLOC of 1.4 Fg/L), indicating that chronic food and drinking water exposures (except possible well contamination), in addition to exposures from mosquitocide abatement and golfing activities do not exceed HED's level of concern. In conclusion, potential **short-term aggregate exposure to chlorpyrifos resulting from food, water and residential/recreational use, assuming the mitigation plan is adopted, does not exceed HED's level of concern.** This analysis is considered conservative because, HED assumed that there could be concurrent residential and recreational exposures to chlorpyrifos (i.e., golfing and mosquitocide abatement activities on the same day). In addition, neither the SCI-GROW model nor the monitoring data reflect concentrations after dilution (from source to treatment to tap) or drinking water treatment.

Table 19
Summary of Short-Term Aggregate Exposure DWLOCs
Chronic Diet and Short-Term Residential Use
Includes Risk Mitigation

Population Subgroup (a)	Acute oral NOAEL (Fg/kg/ day)	Short-Term MOE (Food and Residential) (Fg/kg/day) (a)	MOE Water (b)	Max. Water Exposure (Fg/kg/ day) c)	Surface Water (Monitoring Data) (Fg/L)	Ground Water SCI-GROW, (excluding well contamination) (Fg/L)	Short-Term DWLOC (Fg/L) (d,e,f)
Children (1-6 years)	500	1,200	1,090	0.4587	0.026	0.007 to 0.103	4.5
Children (7-12 years)		1,400	3,450	0.14			1.4
Females (13-50 years)		1,900	2,100	0.238			7.1

(a) Values are from Table 18.
(b) MOE_{WATER} = 1 / [(1/MOE_{AGG} - [1/MOE_{FOOD} + 1/MOE_{DERMAL} + 1/MOE_{ORAL}]), where MOE_{AGG} is 1000.
(c) Maximum Water Exposure (Fg/kg/day) = Acute NOAEL of 500 (Fg/kg/day)÷ MOE_{WATER}
(d) DWLOC (Fg/L) = Maximum water exposure (Fg/kg/day) x body wt (kg) ÷ water consumed daily (L/day)]
(e) HED default body weights are: adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

5.3 Intermediate-Term Aggregate Risk

Based on the mitigation plan, there are no residential/recreational uses that result in exclusively intermediate-term exposures (i.e., > 30 days but less than 6 months). Therefore, an intermediate-term aggregate risk estimate was not evaluated.

5.4 Chronic Aggregate Risk

The chronic aggregate risk estimate to chlorpyrifos addresses exposures from food and drinking water. For the highly refined chronic dietary exposure analysis, PDP, FDA and NFS monitoring data were used to the greatest extent possible, along with field trial data, and cooking and processing factors to assess dietary exposures. This aggregate assessment incorporates the mitigation plan (i.e., reduction of apple tolerance to 0.01 ppm based on dormant application, reduction of grape tolerance to 0.01 ppm based on domestic use pattern and deletion of the use on tomatoes), and assumes there are no chronic exposures from termiticide treatments.

The chlorpyrifos chronic noncancer dietary risk estimates range from 2.5 to 51% of the cPAD, with children (1-6 yrs) being the highest exposed population subgroup. Thus, the chronic dietary (food) risk estimate associated with chlorpyrifos exposure is below the Agency's level of concern.

Using conservative screening-level models the groundwater EECs range from 0.007 to 0.103 Fg/L. The upper-bound surface water EEC, based on monitoring data, is 0.026 Fg/L. As noted previously, DWLOCs were calculated based on food (including food handling establishment uses) and water exposure alone to account for the mitigation options. The chronic non-cancer DWLOC values were presented previously in Table 8, and are shown below on Table 20. For each population subgroup listed, the chronic PAD and the chronic dietary (food) exposure (from Table 4) for that subgroup were used to calculate the chronic DWLOC for the subgroup, using the formulas in footnotes of Table 20. As shown, the upper-bound EEC of 0.103 Fg/L is less than the DWLOCs, and therefore does not exceed HED's level of concern. It should be noted that neither the SCIGROW model nor the monitoring data reflect actual drinking water concentrations after dilution (from source to tap) or drinking water treatment.

Table 20
Summary of Short-Term Aggregate Exposure DWLOCs
Includes Risk Mitigation

Population Subgroup (a)	Chronic PAD (Fg/kg/day)	Chronic Food Exposure with FHE (Fg/kg/day) (b)	Max. Water Exposure (Fg/kg/day) (c)	Surface Water Monitoring Data (Fg/L)	Ground Water SCI-GROW (excluding well contamination) (Fg/L)	Chronic DWLOC (Fg/L) (d,e,f)
U.S. Population	0.3	0.008	0.292	0.026	0.007 to 0.103	10
All Infants (< 1 Year)	0.03	0.01	0.02			0.2
Children (1-6 years)	0.03	0.015	0.015			0.15
Females (13-50 years)	0.03	0.006	0.024			0.72

(a) In addition to the U.S. population (all seasons), the most highly exposed subgroup within each of the infants, children, female groups is listed.
(b) Values are from Table 4 (and rounded).
(c) Maximum Water Exposure (Fg/kg/day) = Chronic PAD (Fg/kg/day) - [Chronic Food Exposure + Chronic Residential Exposure (Fg/kg/day) (if applicable)]. Chronic residential uses were not considered based on mitigation options.
(d) DWLOC (Fg/L) = Maximum water exposure (Fg/kg/day) x body wt (kg) ÷ water consumed daily(L/day)]
(e) HED default body weights are: general U.S. population, 70 kg; adult females, 60 kg; and infants/children, 10 kg.
(f) HED default daily drinking water rates are 2 L/day for adults and 1 L/day for children.

As noted previously, long-term exposure to chlorpyrifos as a result of well contamination from termiticide use could potentially result in exposures of concern. However, the groundwater risk estimates from well contamination resulting from termiticide use are highly localized. The implementation of PR 96-7 for termiticides has reduced the reported incidence of groundwater contamination resulting from termiticide treatments.

Although not all of the risk estimates for termiticide use achieve a margin of exposure of 1000, the Agency believes that individuals are unlikely to experience adverse health effects from the termiticide use of chlorpyrifos. This conclusion is based on: the public health protective assumptions; the 1000 fold safety factor; and the additional 3 to 10 fold cushion between the NOAEL and the LOAEL. Mitigation measures will further reduce exposures and risk associated with the termiticide use. For example, the removal of whole house barrier treatment addressed the exposures of most concern. It is expected that the limited spot and localized treatment, and pre-construction treatments would represent less exposure and risk. In conclusion, based on the mitigation plan, and best professional and scientific judgement, the Agency concludes that the chronic aggregate risk including termiticide use, does not raise a concern.

6.0 Cumulative Exposure and Risks

The Food Quality Protection Act (1996) stipulates that when determining the safety of a pesticide chemical, EPA shall base its assessment of the risk posed by the chemical on, among other things, available information concerning the cumulative effects to human health that may result from dietary, residential, or other non-occupational exposure to other substances that have a common mechanism of toxicity. The reason for consideration of other substances is due to the possibility that low-level exposures to multiple chemical substances that cause a common toxic effect by a common mechanism could lead to the same adverse health effect as would a higher level of exposure to any of the other substances individually. A person exposed to a pesticide at a level that is considered safe may in fact experience harm if that person is also exposed to other substances that cause a common toxic effect by a mechanism common with that of the subject pesticide, even if the individual exposure levels to the other substances are also considered safe.

Chlorpyrifos is a member of the organophosphate (OP) class of pesticides. All pesticides of this class contain phosphorus and other members of this class of pesticides are numerous and include azinphos methyl, chlorpyrifos-methyl, diazinon, dichlorvos, dicrotophos, dimethoate, disulfoton, methamidophos, methidathion, monocrotophos, oxydemeton methyl, phorate, phosmet, and pirimiphos-methyl to name a few. EPA considers organophosphates to express toxicity through a common biochemical interaction with cholinesterase which may lead to a myriad of cholinergic effects and, consequently the organophosphate pesticides should be considered as a group when performing cumulative risk assessments. HED recently published the final guidance that it now uses for identifying substances that have a common mechanism of toxicity (FR 64(24) 5796-5799, February 5, 1999).

HED has recently developed a framework that it proposes to use for conducting cumulative risk assessments on substances that have a common mechanism of toxicity. This framework was presented to the SAP. The SAP was in general agreement with the framework, and made recommendations for improving it. HED plans to release the proposed framework for public comment in March 2000. The framework is available from the Internet at: http://www.epa.gov/scipoly/. In the framework it is stated that a cumulative risk assessment of substances that cause a common toxic effect by a common mechanism will not be conducted until an aggregate exposure assessment of each substance has been completed. The framework is expected to be finalized by the fall of 2000. When the methods are completed and peer reviewed, EPA will proceed with a cumulative assessment of the organophosphates. The current assessment addressed only the risks posed by chlorpyrifos.

7.0 Confirmatory Data

Additional data requirements have been identified in the attached Science Chapters and are summarized here.

7.1 Toxicology Data for OPPTS Guidelines

HED has recommended and the registrant has developed a protocol for a Repeated Exposure Neurotoxicity Study of Sensory Electrophysiology. This study will also include measurement of neurotoxic esterase (NTE). It is expected that this would be a 28 day 2 dose, oral exposure study. In addition to the neurophysiological and neurochemical measures, neuropathological assessment focused on central/peripheral axonopathic changes associated with OPIDN (organophosphate-induced delayed neuropathy should also be performed). This is special study for which no single EPA guideline provides complete guidance. EPA has a guideline for 28 day hen studies of organophosphates that may cause OPIDN that includes guidance for neuropathology and NTE measurements (US EPA 1998; 870.6100). EPA has a guideline for examining peripheral nerve function (US EPA 85-SS1998; 870.6850) and a guideline for sensory evoked potentials (US EPA 1998; 870.6855). The current protocol for this special study has been developed by the registrant working voluntarily in conjunction with EPA. While EPA has not required this study, EPA maintains the right to require further study, based on concerns for potential health effects, consistent with its obligations under FIFRA.

7.2 Product and Residue Chemistry Data for OPPTS Guidelines

7.2.1 Product Chemistry

Forty (40) MP's have been identified. Guideline 830.6314 data requirements remain outstanding for the DAS 99% T. Data remain outstanding for all other chlorpyrifos MPs; for many MPs no product chemistry data have been submitted. The reregistration guidelines for

product chemistry data requirements are complete, provided that the registrants submit the data required in the attached summary tables for the chlorpyrifos MPs, and either certify that the suppliers of starting materials and the manufacturing processes for the chlorpyrifos technicals and manufacturing-use products have not changed since the last comprehensive product chemistry review or submit complete updated product chemistry data packages.

7.2.2 Residue Chemistry

The following confirmatory data requirements and/or label revisions for magnitude of the residue in plants (Guideline 860.1500) remain outstanding or are now required:

- For asparagus, no additional residue data are required. However, a label revision is needed. The maximum equivalent rate of 1.9 lb ai/A specified by a homeowner-use label (EPA Reg. No. 62719-56) should be adjusted to reflect the maximum registered rate of 1.0 lb ai/A for which adequate residue data are available. In a letter to the Agency dated 5/8/95 the registrant committed to correcting the label directions to 1.0 lb ai/A at the next label printing.

- For corn, label restrictions prohibiting feeding of silage, forage, or fodder to meat or dairy animals are not practical and must be removed from SLN DE930004 and FL940003 labels. Additional data must be submitted to determine if established tolerances on corn forage and fodder are adequate for these uses. Alternatively, these SLN uses may be canceled.

- For cotton, feeding restrictions for gin trash (gin by-products) are not practical and must be removed from product labels. Appropriate tolerances for cotton gin by-products must be proposed. The proposal must be supported by adequate residue data conducted according to the maximum use patterns.

- For crops grown solely for seed (clover, and grasses), tolerance proposals and adequate field residue data are required to support SLN (Section 24-c) uses. The Oregon Clover Association has indicated that it will support chlorpyrifos SLN (OR850032) use on clover grown for seed. The requirements specified in the Addendum to the Chlorpyrifos SRR remain outstanding. For grasses grown for seed, appropriate tolerances for residues of chlorpyrifos *per se* in/on grass forage and hay must be proposed. The proposal must be supported by adequate residue data conducted according to the maximum use patterns specified by NV940002, and OR94032.

Alternatively, these SLN uses may be canceled.

- For mint, Table 1 (OPPTS Test Guidelines 860, August 1996) requires data for peppermint and spearmint tops (leaves and stems). Mint hay is no longer considered a RAC. Additional data are required for peppermint and spearmint tops (leaves and stems).

- For peppers, the requirements specified by the Addendum to the Chlorpyrifos SRR to submit English translations of labels for all products that permit use of chlorpyrifos on peppers imported to the U.S. have not been fulfilled. Chlorpyrifos use on peppers was approved at the issuance of the SRR, SLN (FL920007, FL920009, GA930003, and GA930004).

- For sorghum, data are required for aspirated grain fractions.

- For the tree nuts group (almonds, filberts, pecans, and walnuts), the Addendum to the Chlorpyrifos SRR did not require additional data to support the established crop group tolerance. However, an examination of the recently amended labels for the 4 lb/gal EC formulation (EPA Reg. Nos. 62719-23 and 62719-220) indicated that a maximum seasonal rate of 10 lb ai/A was inadvertently approved for pecans. The available residue data, reflecting combined residues of chlorpyrifos and TCP in/on pecans and other representative members of this crop group, only support a maximum seasonal rate of 5 lb ai/A. If the registrant wishes to support a seasonal rate of 10 lb ai/A, then additional data are required. Alternatively, the labels for pecans may be revised to reflect a maximum seasonal rate of 5 lb ai/A. In a letter to the Agency dated 5/8/95, DAS stated that they would modify labels to reflect a maximal seasonal use rate of 5 lb ai/A for pecans at the next label printing. The latest approved label for Lorsban 4E (EPA Reg. No. 62719-220), dated 4/8/96 did not include this modification. The labels should be revised or appropriate residue data supplied.

- For wheat, data are required for aspirated grain fractions.

[Note: The field trial data submitted for asparagus, apples, sugar beets, and tree nuts depict combined residues of chlorpyrifos and TCP. In the absence of adequate data depicting chlorpyrifos *per se* on the commodities of these crops, the established tolerances, for tolerance reassessment purposes, should remain at the existing levels. It is the registrant's prerogative to petition the Agency and submit additional field residue data depicting chlorpyrifos *per se* in/on these crops if tolerance-level reductions or lower anticipated residue calculations are desired.]

GLN 860.1520: Magnitude of the Residue in Processed Food/Feed

According to Table 1 (August 1996) OPPTS 860.1000 Test Guidelines residue data for sorghum flour are not needed at this time because it is used exclusively as a component of drywall, and not as a food or animal feed item, in the US. However, because 50% of the worldwide

sorghum production is used for human consumption, data may be needed at a later time.

The requirements for processing data on alfalfa meal are waived because residue data indicate that levels of chlorpyrifos *per se* are not likely to exceed the established tolerance in alfalfa hay following tests conducted according to registered uses. In addition, no sweet corn processing data are required since adequate corn forage data are available.

The available processing data for apples and sugar beets depict combined residues of chlorpyrifos and TCP. In the absence of adequate data depicting chlorpyrifos *per se* on the processed commodities of these crops, the established feed additive tolerances, for tolerance reassessment purposes, should remain at the existing levels. It is the registrant's prerogative to petition the Agency and submit additional processing data depicting chlorpyrifos *per se* in/on these commodities if tolerance-level reductions or lower anticipated residue calculations are desired.

GLNs 860.1850 and 860.1900: Confined/Field Rotational Crops

Provided that DAS modifies all labels for its chlorpyrifos containing products to limit application to 5 lb ai/A/season on those crops where rotation to another crop could occur (as was stated in their letter to the Agency dated 8/12/94), HED will not require field rotational crop studies. Furthermore, a 30 day plant back interval for rotational crops would then be appropriate.

7.3 Occupational Exposure Data for OPPTS Guidelines

HED has insufficient data for the following agricultural handler scenarios:

- seed treatment uses
- dip applications (e.g., preplant peaches)
- dry bulk fertilizer applications to citrus orchard floors

These scenarios are of concern given the results from the other scenarios assessed.

For postapplication agricultural worker exposures, there is insufficient information (e.g., timing of applications -- dormant/bark versus foliar treatments) and exposure data to assess postapplication activities for ornamental and soil incorporated uses. The data needed to assess these uses include ornamental dislodgeable foliar residues in greenhouses and biological monitoring data for reentry into treated areas with soil directed applications.

In addition, HED could not evaluate the postapplication exposures and risks associated with use of insecticidal dust products due to an absence of chemical-specific data or recommended procedures in the Residential SOPs. Nevertheless, HED has concerns about the use of these products based on the low MOEs calculated using the surrogate data from the scientific literature for residents or workers that could apply these products. HED recommends that the registrant provide additional information on the potential post-application residential exposures associated with these products.

HED requests additional data for indoor crack, crevice and spot uses of chlorpyrifos. Specifically, HED requests treated room residue data for floors, furniture and other surfaces available for contact by children for both chlorpyrifos, and its primary degradation metabolite, 3,5,6-TCP following multiple treatments. Additionally, HED requests chlorpyrifos air measurements in treated rooms following multiple treatments (i.e., at a minimum 3 treatments 7 days apart). Residue data for 3,5,6-TCP are important due to the potential for accumulation and persistence of this environmental degradate.

HED requests confirmatory air monitoring data immediately following ground-based fogger application due to potential concern for short-term inhalation exposures.

In addition, HED requests exposure and/or environmental data for all registered products and/or uses that are not assessed in this risk assessment.

8.0 References

Adgate, J., Quackenboss, J, Needham, L., Pellizari, P., Lioy, P, Shubat, P., and Sexton, K . 1998. Comparison of Urban versus Rural Pesticide Exposure in Minnesota Children. Annual Conference of International Society for Environmental Epidemiology (ISEE) and International Conference for Society of Exposure Analysis (ISEE). July 1998, Volume 9 No. 4. Supplement. Abstract 92 O.

Blondell, J., and Dobozy, 1997. Memorandum to Linda Propst: Review of Chlorpyrifos Poisoning Data. January 14, 1997. U.S. Environmental Protection Agency, Washington, D.C.

Buckley T.J., Liddle J., Ashley D.L., Paschal D.C., Burse V.W., Needham L.L., and Akland G. 1997. Environmental and Biomarker Measurements in Nine Homes in the Lower Rio Grande Valley: Multimedia Results for Pesticides, Metals, PAHs and VOCs. Environmental International. 23(5):705-732.

Campbell, C.G., Seidler, F.J, and Slotkin, T.A. (1997). Chlorpyrifos interferes with cell development in rat brain regions (Brain Res. Bull 43(2):179-189.

Capodicasa, E., Scapellato, M.L., Moretto, A., Caroldi S., and Lotti, M. 1991.

Chlorpyrifos-induced delayed polyneuropathy. Arch Toxicol. 65:150-155.

Chanda, S.M., Mortensen, S.R., Barone, S., Moser, V.C., and Padilla, S. 1997. Developmental Profiles of two organophosphate detoxifying enzymes: carboxylesterase and A-esterase [abstract 1757]. Toxicologist 36(1):346.

Costa LG, Li WF, Richter RJ, Shih DM, Lusis A, and Furlong CE. 1999. The role of paraoxonase (PON1) in the detoxication of organophosphates and its human polymorphism. Chemico-Biological Interactions 119-120: 429-438

Coulston, F., Golberg, L. and Griffin, T. 1972. Safety Evaluation of DOWCO 179 in Human Volunteers. Institute of Experimental Pathology and Toxicology, Albany Medical College, Albany, New York. MRID No. 95175. HED Doc No. 000179, 03822, 04363.

Dam K, Garcia SJ, Seidler FJ, Slotkin TA (1999a) Neonatal chlorpyrifos exposure alters synaptic development and neuronal activity in cholinergic and catecholaminergic pathways. Developmental Brain Res. 116:9-20.

Dam K; Seidler FJ; Slotkin TA (1999b) Chlorpyrifos releases norepinephrine from adult and neonatal rat brain synaptosomes. Brain Res Dev Brain Res, 118(1-2):129-33.

Das KP, Barone S (1999) Neuronal differentiation in PC-12 cells is inhibited by chlorpyrifos and its metabolites: Is acetylcholinesterase inhibition the site of action? Toxicol. Applied Pharmacol. 160:217-230.

Davies HG, Richter RJ, Keifer M, Broomfield CA, Sowalla J, and Furlong CE. 1996. The effect of the human serum paraoxonase polymorphism is reverse with diazoxon, soman and sarin. Nat Genet. Nov 14(3):334-6.

Dittenber, D.A 1997. Chlorpyrifos: Evalauation of Single Oral Doses on Cholinesterase and Neurotoxic Esterase Inhibition in F344 Rats. Toxicology Laboratory, Dow Chemical Co. Study No. 960036. March 13, 1997. MRID No. 44273901.

Dow AgroSciences. 1998. Chlorpyrifos Technical Bulletin: Toxicity. Urban Exposure Considerations. Dow AgroSciences LLC. Indianapolis, IN. July.

EPA 1992. National Study of Chemical Residues in Fish. Office of Science and Technology (WH-551), Washington, D.C. Office of Water. EPA 823-R-92-008a. September 1992.

EPA 822-R-96-001; Drinking Water Regulations and Health Advisories; Office of Water; February 1996.

Food and Drug Administration (FDA). 1999. Total Diet Study. Summary of Residues Found Ordered by Pesticide Market Baskets 91-3 - 97-1. June, 1999.

Furlong, CE., Li WF., Costa, LG., Richter RJ., Shih DM, and Lusis AJ. 1998 Genetically determined susceptibility to organophosphorus insecticides and nerve agents: developing a mouse model for the human PON1 polymorphism. Neurotoxicology. Aug-Oct: 19(4-5):645-60

Hill R.H., Head, S.L., Baker, S., Gregg, M., Shealy, D.B., Bailey, S.L., Williams, C.C., Sampson, E.J., and Needham, L.L. 1995. Pesticide Residues in Urine of Adults Living in the United States: Reference Range Concentrations. Environmental Research. 71:99-108.

Hoberman A.M. 1998a,b. Developmental neurotoxicity study of chlorpyrifos administered orally via gavage to Crl:CD®BR VAF/Plus® presumed pregnant rats. Argus Research Laboratories, Inc., Horsham, Pennsylvania, laboratory study No. 304-001, sponsor study No. K-044793-109, May 1, 1998: MRID 44556901, MRID 44661001.

Jefferson Davis Associates, Inc. 1999. Lawn Care Applicator Exposure to Dursban. A Study of Typical Treatment Practices. A Quantitative Study. Prepared for Dow AgroSciences. December 1999.

Jett D.A., Navoa, R.V., Lyons, M.A. 1999. Additive inhibitory action of chlorpyrifos and polycyclic aromatic hydrocarbons on acetylcholinesterase activity in vitro. Toxicology Letters. 105:223-229.

Johnson, D.E., Seidler F.J., and Slotkin, T.A. 1998. Early Biochemical Detection of Delayed Neurotoxicity Resulting from Developmental Exposure to Chlorpyrifos. Brain Research Bulletin. 45(2):143-147.

Kilburn KH. 1999. Evidence for chronic neurobehavioral impairment from chlorpyrifos an organophosphate insecticide (Dursban) used indoors. Environmental Epidemiology and Toxicology 1:153-162.

Kisicki J.S., Seip, C.W., and Combs M.L. 1999. A Rising Dose Toxicology Study to Determine the No-Observable-Effect-Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels. MDC Harris Laboratory, Lincoln Nebraska, Study No. 21438 (for the Harris Project) and DR K-0044793-284 (for Dow AgroSciences), April 19, 1999, MRID No. 44811002.

Lassiter TL, Padilla S, Mortensen SR, Chanda SM, Moser VC, Barone S (1998) Gestational exposure to chlorpyrifos: Apparent protection of the fetus? Toxicol. Applied Pharmacol. 152: 56-65.

Li WF, Costa LG, Furlong CE. 1993. Serum paraoxonase status: a major factor in determining resistence to organophosphates. J Toxicol Environ Health. Oct-Nov: 40(2-3):337-46.

MacIntosh D.L., Needham L.L., Hammerstrom K.A., and Ryan P.B. 1999. A longitudinal investigation of selected pesticide metabolites in urine. J. of Exposure Analysis and Environ Epidem. 9:494-501.

Mattsson J.L., Maurissen J.P., Spencer, P.J., Brzak K.A., and Zablotny C.L. 1998. Effects of Chlorpyrifos administered via gavage to CD rats during gestation and lactation on plasma, erythrocyte, heart and brain cholinesterase and analytical determination of chlorpyrifos and metabolites. Health and Environmental Research Laboratories, The Dow Chemical Co. for Dow AgroSciences, August 31, 1998. Unpublished Study. MRID 44648101.

Maurissen J.P., Shankar, M.R., Mattsson J.L. 1996. Chlorpyrifos: cognitive study in adult Long-Evans rats. The Toxicology Research Laboratory, Health and Environmental Studies, The Dow Chemical Co. Midland, MI. Laboratory Project Study ID K-044793-096. April 29, 1996. MRID No. 44020901. Unpublished.

Mendrala A.L., and Brzak K.A. 1998. Chlorpyrifos: Part A-concentration-time course of chlorpyrifos and chlorpyrifos-oxon in blood. Health and Environmental Research Laboratories. The Dow Chemical Co. Midland MI. Laboratory Project Study ID: 971187A. August 31, 1998. MRID No. 44648102. Unpublished.

Mortensen, S.R., Hooper M.J. S. Padilla. 1998. Rat brain acetylcholinesterase activity: developmental profile and maturational sensitivity to carbamate and organophosphorus inhibitors. Toxicology. 125:13-19.

Moser, V.C. and S. Padilla. 1998. Age- and gender-related differences in the time-course of behavioral and biochemical effects produced by oral chlorpyrifos in rats. Toxicology and Applied Pharmacology. 149:107-119.

Moser, V.C., Chanda, S.M., Mortensen S.R., and Padilla, S. 1998. Age- and Gender-Related Differences in Sensitivity to Chlorpyrifos in the Rat Reflect Developmental Profiles of Esterase Activities. Toxicological Sciences. 46:211-222.

Nolan R.J., Rick D.L., Freshour M.L., and Saunders J.H. 1982. Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses. The Dow Chemical Co. Biomedical Medical Research Lab. Toxicology Research Lab. Midland MI. Accession No. 249203.

Pope, C.N., Chakraborti, T.K., Chapman, M.L., Farrar, J.D., and Arthur, D.(1991). Comparison of in vivo Cholinesterase Inhibtion in Neonatal and Adult Rats by Three Organophosphorothioate Insecticides. *Toxicology*

Pope, C.N and Liu, J (1997). Age-Related Differences in Sensitivity to Organophosphorous Pesticides. *Environmental Toxicol. And Pharmacol.* 4;309-314.

Quackenboss, J.J., Pellizari, E., Freeman, N., Head, S., Whitmore, R., Zelon, H., Stroebel, C. 1998. Use of Screening Questionnaires to Identify Exposed and Sensitive Population Groups in the Region V NHEXAS Children's Pesticide Study. Annual Conference of International Society for Environmental Epidemiology (ISEE) and International Conference for Society of Exposure Analysis (ISEE). July 1998, Volume 9 No. 4. Supplement. Abstract 440 O.

Roy TS, Andrews JE, Seidler FJ, Slotkin TA (1998) Chlorpyrifos elicits mitotic abnormalities and apoptosis in neuroepithelium of cultured rat embryos. Teratology 58:62-68.

Shih DM, Gu L, Xia YR, Navab M, Li WF, Hama S, Castellani LW, Furlong CE, Costa LG, Fogelman AM and Lusis AJ. 1998. Mice Lacking serum paraoxonase are susceptible to organophosphate toxicity and atherosclerosis. Nature. Jul 16: 394 (6690):284-7

Slokin T.A. 1999. Developmental Cholinotoxicants: Nicotine and Chlorpyrifos. Environmental Health Perspectives. 107, Supplement 1, 71-80.

Song, X., Seidler, F.J., Saleh, J.L., Zhang, J. Padilla, S., Slotkin T.A. 1997. Cellular mechanisms for developmental toxicity of chlorpyrifos: targeting the adenylyl cyclase signaling cascade. Toxicol Appl. Pharmacol. 145:158-174.

Steenland K., Dick RB., Howell RJ., Chrislip DW., Hines CJ., Reid TM., Lehman E., Laber P., Krieg EF. Jr., Knott C. 2000. Neurologic function among termiticide applicators exposed to chlorpyrifos. Environmental Health Perspectives. 108(4):293-300. February.

Tang J, Cao RL, Chambers JE (1999) Changes in rat brain cholinesterase activity and muscarinic receptor density during and after repeated oral exposure to chlorpyrifos in early postnatal development. Toxicological Sciences 51:265-272.

Tietz, N.W. 1982. Fundamentals of Clinical Chemistry, 3rd Edition, W.B., Saunders Company, Philadelphia, PA. pg. 1950.

TruGreen/ChemLawn. 1999. Comments Submitted during Phase 2 Public Comment Period. November 29, 1999. Includes letter from R.A. Yeary, and studies of Pesticide Exposure of ChemLawn Employees 1975-1983.

U.S. Environmental Protection Agency. 1992. National Study of Chemical Residues in Fish. Volume 1. Office of Science and Technology. WH-551. Washington DC. EPA 823-R-92-008a. .

U.S. Environmental Protection Agency. 1997. Exposure Factors Handbook. Volume 1. General Factors. Office of Research and Development. Washington, D.C. Page 1-7. EPA/600/P-95/002Fa.

Whitney, K.D., Seidler, F.J., and Slotkin, T.A (1995). Developmental Neurotoxicity of

Chlorpyrifos Cellular Mechanism.*Toxicol. And Pharmacol*134:53-62

Wright, C.G., Leidy, R.B., and Dupree, H.E., Jr. 1988. Chlorpyrifos in the Ambient Air of Houses Treated for Termites. Bull. Environ. Contam. Toxicol. 40:561-568.

Wright, C.G., Leidy, R.B., and Dupree, H.E., Jr. 1994. Chlorpyrifos in the Air and Soil of Houses Treated Eight Years after its Application for Termite Control. Bull. Environ. Contam. Toxicol. 52:131-134.

Zheng, Q., Olivier K., Won Y., and Pope C. 1999. Comparative Cholinergic Neurotoxicity of Oral Chlorpyrifos Exposures in Neonatal and Adult Rats. Abstract and Poster Presentation. presented at the 38th Annual Society of Toxicology Meeting in New Orleans, March 14-18. The Toxicologist Vol 48, No.1-S, #874. March 1999.

Zheng Q, Olivier K, Won YK, Pope CN (2000) Comparative cholinergic neurotoxicity of oral chlorpyrifos exposures in preweanling and adult rats. Toxicological Sciences. 55:124-132.

APPENDIX A: Sensitivity/Susceptibility of the Young

The following summary has been extracted from the following report: "Chlorpyrifos Children's Hazard: Sensitivity and Susceptibility" HED Doc No. 014074, March 28, 2000. The entire document is also an appendix to the April 6, 2000 HIARC report (which is an attachment to the risk assessment).

The weight of evidence provides appreciable support for the increased sensitivity of the young compared to adult rats to the neurotoxic effects of chlorpyrifos and for the susceptibility of the developing brain to chlorpyrifos. A number of different rat studies clearly demonstrate that at a given oral dose the young rat will respond more to the anticholinesterase effects of chlorpyrifos (as defined biochemically and behaviorally) than adult animals. The differential found between pups and adult animals is a function of the treatment dose, duration of treatment, timing of treatment (*i.e.*, developmental stage) and of measurements (*i.e.*, time to peak effect), and the toxicological endpoint examined. At high acute doses, chlorpyrifos is fatal to the rat pup, but produces no lethality and little to no behavioral changes in the adult rat (*e.g.*, LD_{10} and MTD doses = neonate-15 mg/kg; adult-136 and 100 mg/kg, respectively). At the LD_{10} or MTD doses neonates are up to ~5-fold more sensitive than adult rats to ChEI (brain and blood) and clinical/behavioral effects. Furthermore, at a single treatment of 15 mg/kg, the down-regulation of the cholinergic (muscarinic) receptors was more extensive in the pups than in adults treated with 80 mg/kg. The magnitude of change, the effective time points, and the brain regions involved were different in pups versus adult rats. This suggests that the cholinergic receptors are more readily altered in the pup following chlorpyrifos treatment. Although the consequence of this is unknown, cholinergic receptors play an important role in normal brain development.

The increase in sensitivity between young and adult animals appears to occur at acute doses below 15 mg/kg. The study by Zheng *et al.* (2000) using lower dose levels (ranging from 0.15 mg/kg to 15 mg/day) provides cholinesterase inhibition (ChEI) data in 7-day old animals and adult male rats showing a greater sensitivity (up to ~3-fold for RBC and plasma, and perhaps at least 5-fold for brain) of pups compared with adult males. In the Zheng *et al.* study, the adult did not respond at the high dose of 15 mg/kg for brain ChEI. Thus, a difference in response greater than 5-fold can not be ruled out. Because of the lack of data, the extent of differences in brain ChEI between pups and the pregnant female rat remains uncertain. Although the young animal appears to recover at least two times faster than the adult animal from the ChEI induced by acute chlorpyrifos treatment, other toxicities (*e.g.,* delays in brain development, behavioral effects) may persist or appear at later times.

Repeated dosing with chlorpyrifos does not appear to result in an increase in brain or blood ChEI in neonates relative to adults with one exception. Based on $ED_{50's}$, there is a 1.5-fold difference in the response of PND 7 pups to brain ChEI compared to adult males (Zheng *et al.,* 2000). In contrast to the rapid recovery from ChEI observed with acute chlorpyrifos treatments of neonates (Pope and Liu, 1997), repeated dosing with

chlorpyrifos (every other day, 11 treatments during PND 1 to PND 21) indicates ChEI persists for ~9 to >19 days depending on the dose administered (Tang *et al.,* 1999). Body weight changes and behavioral effects occur at ~3-fold lower doses in neonates versus adult rats with repeated treatments of chlorpyrifos doses equal to or above 3 mg/kg/day.

It is apparent that cholinesterase activity is inhibited in the fetus if the dam is treated with a chlorpyrifos dose which can be absorbed by the fetus. The magnitude of brain, plasma, and RBC ChEI in the fetus is less or equal to that observed in dams with acute or repeated treatments of dams with chlorpyrifos. The lack of an apparent differential response of the fetus (or neonate with repeated dosing) versus the maternal system to treatment of dams with chlorpyrifos may be due to the increased new synthesis or more rapid turnover of inhibited molecules of cholinesterases in the fetal brain than in the adult (Lassiter *et al*., 1998; Mortensen *et al*., 1998).

Differences in detoxification between the young and adults may explain the increased sensitivity of exposed pups to chlorpyrifos toxicity. Chlorpyrifos and its oxon *(i.e.*, the anticholinesterase metabolite) are detoxified by binding to carboxlyesterases and hydrolysis by A-esterases. The young animal has minimal activity of these detoxification enzymes compared to adult animals. The precise influence of these enzymes on sensitivity to chlorpyrifos treatment has not been established. Because detoxification enzyme activities increase with age, the enzymatic profile of newborn rats raises concern that the newborn may be even more sensitive than older neonates to an acute chlorpyrifos treatment. There is some evidence (albeit at high doses) that suggests that the magnitude of the differential sensitivity between young and adult animals depends on the age of the animal. Based on the LD_{10} data in Zheng *et al.* and from the ChEI data in Zheng *et al.* and Moser and Padilla (1998), the order of sensitivity is PND 7 > PND 17 > PND 27 > adult female > adult male. Therefore, given that 7-day old rats are the youngest animals evaluated to date, it is uncertain whether the magnitude of differential sensitivity would be greater with pups exposed earlier than 7 days.

The developmental neurotoxicity study, which involved treatment of dams with 5, 1, or 0.3 mg/kg/day chlorpyrifos from GD 6 through lactation day 11 (Hoberman, 1998a,b), offspring were observed to have alterations in brain structure that are suggestive of a developmental defect that may predispose the neonate to unique adverse consequences. In this study, morphometric measurements in PND 11 pups of the high dose included, decreases in anterior to posterior measurements of the cerebellum, reduced height of the cerebellum, decreased thickness of the parietal cortex, and decreased thickness of the hippocampal gyrus. These effects at the high dose occurred in the presence of maternal toxicity (*e.g*., maximum brain, RBC and plasma ChEI) but in the absence of effects on body weights, food consumption, pregnancy parameters, or deaths among the dams. In mid- and high-dose PND 66 offspring, effects on brain structure included marginal but statistically significant decreases in the thickness of the parietal cortex and non-significant decreases in the thickness of the hippocampal gyrus. This difference in the qualitative severity of the findings seen in adult and neonatal animals is indicative of susceptibility of the offspring. It is also important to note that morphometric evaluation of the low-dose

brains was not conducted. So it is not known whether alterations are occurring at lower doses.

Additionally, a number of the treatment-related findings in the offspring appear to be delayed in expression of perturbations in earlier neurological development, because functional and morphological changes are observed at study termination (~PND 61 - 66), approximately 50 - 55 days after cessation of maternal dosing. At the high dose, these findings included increased motor activity in females at PND 61, alterations in auditory startle measurements (increased latency to peak response and decreased peak response amplitudes) at PND 62, and morphometric alterations in the parietal cortex and hippocampal gyrus on PND 66.

A variety of *in vitro* and *in vivo* studies published in the peer reviewed literature show that chlorpyrifos can alter macromolecular synthesis, neuronal activity, neurotransmitter levels, neurite outgrowth and branching, and cell signaling in the developing rat brain (reviewed by Slotkin, 1999). Although these studies did not include accompanying measures of direct adverse effects (*e.g.,* functional effects) but rather used biomarkers, they nevertheless raise concern that chlorpyrifos potentially can affect processes occurring in both early and late developmental periods of brain growth that influence cell replication and differentiation needed for normal function. Although the data primarily come from one laboratory, multiple studies from this group have shown a consistency in the different responses measured. Furthermore, several of the key responses observed are highly significant and robust (*e.g.,* effects on norepinephrine turnover, DNA synthesis, adenylyl cyclase transduction). Also, the responses reported tend to have little variability in the data. Finally, effects on the developing brain reported in the literature are consistent with the morphometric changes observed in the guideline developmental neurotoxicity study by Hoberman (1998) even though a direct linkage of effects can not be made. The available data suggest a selective action of chlorpyrifos on the developing brain, given the regional and temporal pattern of responses. Thus, it seems unlikely that the observed effects are due to nonspecific toxicity.

Although there are strengths of these studies, there are also some limitations and questions raised which are not addressed by the results. As discussed above, the mechanism of action for chlorpyrifos in the developing brain is unclear. Also, the *in vivo* studies using macromolecular biomarkers have primarily been conducted using the subcutaneous injection (SC) route of exposure and DMSO as the vehicle. It should be noted that DMSO controls were conducted in all the studies. DMSO would result in a rapid uptake and full absorption of the compound. Compounds administered via SC injection enter directly into the general circulation and bypass hepatic metabolism once, thus bypassing hepatic activation of chlorpyrifos to its active metabolite chlorpyrifos-oxon. The SC route of exposure can not be reliably compared to the oral route given the lack of pharmacokinetic data on this dosing regime. Also, this is not a pathway of human exposure. Thus the DMSO-SC dosing regime makes quantitative interpretation and extrapolation of the results problematic. Nevertheless, these studies still provide important qualitative information on the potential for chlorpyrifos to affect neurodevelopmental processes. Cholinesterase inhibition was not measured in most of these studies except for Song *et al.* (1997). In that study, no extreme cholinesterase inhibition is found in the brainstem at the low dose used in the study: approximately 20-25% cholinesterase

inhibition is found when 1 mg/kg of chlorpyrifos is administered during PND 1-4 and cholinesterase activity (measured 24 hours after the last dose) is almost completely recovered by 10 days of age (Song *et al.*, 1997). Given that key effects in the postnatal brain are found at the low dose, the concern of a rapid delivery of a toxic dose with this standard dosing regime is reduced. Also, no significant changes in body or brain weight and no mortality occurs with this dosing regime (1 mg/kg at PND 1-4 or 5 mg/kg at PND 11-14). Additionally, it should be noted that chlorpyrifos is rapidly absorbed and transported to the brain with oral dosing (Mendrala and Brzak, 1998). Thus, the findings derived from the SC/DMSO dosing regime can not be discounted as an artifact of the vehicle and route of exposure and raise concerns for the unique susceptibility of the young.

The mechanism(s) of action for the chlorpyrifos-induced changes (*e.g.,* macromolecular synthesis, cell signaling) is/are unclear. However, given that these effects can be found after intracisternal injection of chlorpyrifos, with *in vitro* TCP treatment, and *in vitro* PC12 cell cultures with limited capability to activate chlorpyrifos to its ChE-inhibiting oxon, raises the issue of whether these effects can occur independent of cholinesterase inhibition. Although it is not possible to link each effect reported with another effect or with a functional outcome, the data show a consistent pattern of the potential for chlorpyrifos to produce qualitatively different effects in the central nervous system (CNS) of young versus adult animals. Potential implications of the effects include alteration of synaptic responses that are programmed by neural input, disruption of cell replication and differentiation, and temporary or persistent delays in the development of CNS structures.

In conclusion, the weight of the evidence raises concern for an increase in both the sensitivity and susceptibility of the fetus or young animal to adverse biochemical, morphological, or behavioral alterations from chlorpyrifos treatment during brain development. With respect to cholinesterase inhibition, an increase in sensitivity of the young compared to adults was seen all along the dose response curve, even at relatively low doses. There is a clear differential response (2- to ~5-fold) in the young compared to the adult animal after an acute treatment to a relatively low dose of chlorpyrifos. There is also increased sensitivity found after repeated dosing (up to 9-fold), but at the LD_{10} and MTD. It is important to point out that an uncertainty remains concerning the magnitude of the differential response, given that newborn animals (less than PND 7) have not been characterized for sensitivity. Results of multiple studies have consistently shown that the developing brain is susceptible to chlorpyrifos treatment. Effects on the developing CNS that are indicative of the unique susceptibility to the young animal include changes in macromolecular synthesis, altered cell signaling and muscarinic receptor down-regulation, as well as morphological alterations in brain development. An uncertainty remains regarding the NOAELs for the susceptibility effects. The effects observed raise a high degree of concern that the fetus or young animal is particularly susceptible to adverse outcome if exposed to chlorpyrifos.

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EPA United States Environmental Protection Agency

Revised Human Health Risk Assessment on Chlorpyrifos

Related Information

- Read the OPP Update
- Basic information on chlorpyrifos uses and EPA actions
- Read the Federal Register notice announcing our denial of a petition to revoke chlorpyrifos tolerances

In November 2016, we revised our human health risk assessment and drinking water exposure assessment for chlorpyrifos. The revised analysis shows risks from dietary exposure (i.e., residues of chlorpyrifos on food crops) and drinking water. Currently, chlorpyrifos remains registered as it undergoes registration review. As part of the ongoing registration review, we will continue to review the science addressing neurodevelopmental effects and complete our assessment by October 1, 2022.

View the 2016 revised human health risk assessment and the refined drinking water assessment. These analyses were available for a 60-day comment period in docket EPA-HQ-OPP-2015-0653 at www.regulations.gov.

Learn more about the revised risk assessment on chlorpyrifos:

1. What does EPA's revised human health risk assessment show?
2. What are EPA's next steps?
3. How did EPA assess risks?
4. Did EPA take into account the 10X safety factor specified under the Food Quality Protection Act to protect children?
5. Can chlorpyrifos affect wildlife?

1. What does EPA's revised human health risk assessment show?

This assessment shows dietary and drinking water risks for the current uses of chlorpyrifos. Based on current labeled uses, the revised analysis indicates that expected residues of chlorpyrifos on food crops exceed the safety standard under the Federal Food, Drug, and Cosmetic Act (FFDCA). In addition, the majority of estimated drinking water exposure from currently registered uses, including water exposure from non-food uses, continues to exceed safe levels, even taking into account more refined drinking water exposure. This assessment also shows risks to workers who mix, load and apply chlorpyrifos pesticide products.

2. What are EPA's next steps?

In March 2017, EPA denied a petition asking us to revoke all pesticide tolerances (maximum residue levels in food) for chlorpyrifos and cancel all chlorpyrifos registrations. We will continue to review the science addressing neurodevelopmental effects of chlorpyrifos as part of the ongoing registration review and complete our assessment by the statutory deadline of October 1, 2022. Read the Federal Register notice announcing our response to the petition.

As part of the ongoing registration review for chlorpyrifos, EPA is also assessing the potential ecological risks from chlorpyrifos. In January 2017, we completed the biological evaluation and initiated formal consultation with the Fish and Wildlife Service and National Marine Fisheries Service. View the final biological evaluation for chlorpyrifos.

3. How did EPA assess risks?

This was one of the first risk assessments to employ a physiologically-based pharmacokinetic and pharmacodynamic (PBPK/PD) model. This is a mathematical model that enhances our ability to assess risk by allowing us to consider variations in a chemical's effects on a person based on such variables as age and genetics and allows us to predict how the same dose may affect various members of a large population differently. EPA has held several meetings of the FIFRA Scientific Advisory Panel to get independent advice on the relevance and usefulness of a PBPK/PD model in assessing a chemical's risks, including one meeting specifically on PBPK/PD and chlorpyrifos.

The 2014 revised human health risk assessment used dose-response data on acetylcholinesterase inhibition (AChI) in laboratory animals to derive a point of departure. However, EPA believes that evidence from epidemiology studies indicates effects may occur at lower exposures than indicated by the toxicology database. The 2016 revised human health risk assessment uses neurodevelopmental effects as the critical effect, taking into account recommendations from the 2016 chlorpyrifos SAP on deriving a point of departure for risk assessment. For additional details on how EPA assessed risks, please see revised risk assessment.

4. Did EPA take into account the 10x safety factor specified under the Food Quality Protection Act to protect children?

Yes, EPA did retain the 10x factor for this risk assessment.

5. Can chlorpyrifos affect wildlife?

Yes, and EPA has taken actions to help protect wildlife from chlorpyrifos exposure. For example, many of the reported incidents of wildlife mortality associated with chlorpyrifos use were related to residential lawn and termite uses and use on golf courses. The residential uses have been eliminated; termiticide uses have been restricted; and the application rate on golf courses has been reduced. Additionally, no-spray buffers around surface water bodies, as well as rate reductions for agricultural uses, further reduced the environmental burden of chlorpyrifos.

The agency is currently consulting with the U.S. Fish and Wildlife Services and the National Marine Fisheries Services to evaluate potential impacts on endangered species.

LAST UPDATED ON APRIL 26, 2017

SINCE 1828

leave

verb (1)
Save Word
\ ˈlēv \
left\ ˈleft \; leaving

Definition of *leave*

(Entry 1 of 3)

transitive verb

1a(1) **:** bequeath, devise *left* a fortune to his son
(2) **:** to have remaining after one's death leaves a widow and two children
b **:** to cause to remain as a trace or aftereffect oil leaves a stainthe wound *left* an ugly scar
2a **:** to cause or allow to be or remain in a specified condition leave the door openhis manner *left* me cold
b **:** to fail to include or take along *left* the notes at homethe movie leaves a lot out
c **:** to have as a remainder 4 from 7 leaves 3
d **:** to permit to be or remain subject to another's action or control just leave everything to me
e **:** let

f **:** to cause or allow to be or remain available leave room for expansion*left* myself an out
3a **:** to go away from **:** depart leave the room
b **:** desert, abandon *left* his wife
c **:** to terminate association with **:** withdraw from *left* school before graduation
4 **:** to put, deposit, or deliver before or in the process of departing I *left* a package for youleave a message

intransitive verb

: set out, depart *left* for the office at eight sharp
leave alone
: to refrain from bothering, disturbing, or using *Leave him alone* while he's doing his homework.

leave

noun

Definition of *leave* (Entry 2 of 3)

1a **:** permission to do something
b **:** authorized especially extended absence from duty or employment
2 **:** an act of leaving **:** departure

leave

verb (2)
leaved; leaving

Definition of *leave* (Entry 3 of 3)

intransitive verb

: leaf

Other Words from *leave* Synonyms Leave vs. Let: Usage Guide More Example Sentences Learn More about *leave*

Keep scrolling for more

Other Words from *leave*

Verb (1)

leaver noun

Synonyms for *leave*

Synonyms: Noun

- break,
- holiday
- [chiefly British],
- hols
- [British],
- recess,
- vacation

Visit the Thesaurus for More »

Leave vs. Let: Usage Guide

Verb (1)

Leave (sense 2e) with the infinitive but without *to leave* it be is a mostly spoken idiom used in writing especially for humorous effect. It is not often criticized in British English, but American commentators, adhering to an opinion first expressed in 1881, still dislike it.

Examples of *leave* in a Sentence

Noun He took an unpaid *leave* from work. The soldiers were given a two-month *leave* for the holidays. He took a few months' *leave* to care for his sick mother. Our professor is *on leave* this semester. She is *on leave* from her law firm. a soldier *on* military *leave* I beg *leave* to differ with you, sir. He was found guilty but was granted *leave* to appeal against the verdict.
See More
Recent Examples on the Web: Verb Several nearby streets will also be available for parking, though drivers may be charged to *leave* their cars in private lots.— Lucas Aulbach, *The Courier-Journal*, "What will the 2021 Kentucky Derby look like? Parking, traffic, COVID safety and dining," 13 Apr. 2021 Once paramedics arrived, Potter ordered both of the officers to *leave* the house, sit in separate squad cars and deactivate their body cameras.— *Washington Post*, "Officer Kim Potter fatally shot Daunte Wright, police said. She's a 26-year vet, served as union president," 13 Apr. 2021 Almost all of the additional 8,500 foreign troops in Afghanistan from NATO allies and other countries are also likely to *leave* in coming months, officials said.— *Los Angeles Times*, "Biden plans to withdraw troops from Afghanistan by Sept. 11," 13 Apr. 2021 Did anyone expect Horschel to *leave* his shoes on while playing from the water?— Paul Daugherty, *The Enquirer*, "Doc's Morning Line: Will the next UC Bearcats men's basketball coach be one of these four?," 13 Apr. 2021 According to recent surveys, 25 to 50 percent of employees plan to *leave* their employers in 2021.— *Anchorage Daily News*, "5 steps you can take to regain your employees' trust," 13 Apr. 2021 People were only allowed to *leave* the house for essential reasons, such as outdoor exercise with one other person, or visiting a place of worship.— *CNN*, "Travel to the UK during Covid-19: What you need to know before you go," 13 Apr. 2021 The late dissident Yelena Bonner, for example, persuaded the late oligarch Boris Berezovsky to *leave* the country rather than risk arrest.— Masha Gessen, *The New Yorker*, "Why Alexey Navalny Returned to Russia," 13 Apr. 2021 During that quarantine, recruits are housed with a roommate but not allowed to *leave* their rooms.— Andrew Dyer, *San Diego Union-Tribune*, "Public recruit graduations will resume at San Diego boot camp, Marines say," 12 Apr. 2021 Recent Examples on the Web: Noun Britt Reid was an assistant with the Chiefs and was placed on administrative *leave* after the crash.— Ryan Gaydos, *Fox News*, "Britt Reid crash victim 'cannot walk, talk or eat like a normal 5-year-old,' cousin says," 14 Apr. 2021 Elliott had advocated for the officer to be put on administrative *leave* as the state Bureau of Criminal Apprehension investigated.— *NBC News*, "Officer who fatally shot Daunte Wright, police chief resign in Brooklyn Center, Minnesota," 14 Apr. 2021 Officials have not publicly identified the officer, who has been placed on administrative *leave* for 30 days.— Christine Fernando, *USA TODAY*, "Family of Adam Toledo views footage of fatal Chicago police shooting of 13-year-old; video will not be immediately released," 14 Apr. 2021 Alvarez-Glasman confirmed that a number of employees were placed on administrative *leave* but would not provide more details, citing the need for confidentiality.— Adam Elmahrek, *Los Angeles Times*, "Several Huntington Park finance employees put on leave, one arrested in data breach probe," 14 Apr. 2021 The trooper involved, who was not identified, was not injured and has been put on administrative *leave* pending an investigation, Jones said.— Rebekah Riess, *CNN*, "A state trooper shot and killed a 16-year-old armed with a knife and airsoft gun, Maryland authorities say," 14 Apr. 2021 Minutes later, the unnamed officer, who is on administrative *leave* pending an investigation, arrived on the scene where Ham allegedly had an airsoft gun and a knife.— Mike Brest, *Washington Examiner*, "Police officer fatally shoots 16-year-old allegedly wielding airsoft gun that's 'a close representation' to a real gun," 14 Apr. 2021 Sheskey was placed on administrative *leave* soon after the shooting as the Wisconsin Department of Justice conducted a months-long investigation.— *Washington Post*, "Kenosha officer who shot Jacob Blake returns to work after internal probe finds 'he acted within the law'," 14 Apr. 2021 Hamilton, who has been with the Escondido Police Department for about four years, was placed on administrative *leave* following the shooting.— City News Service, *San Diego Union-Tribune*, "Man who ran at Escondido officer with crowbar sentenced to prison," 13 Apr. 2021

These example sentences are selected automatically from various online news sources to reflect current usage of the word 'leave.' Views expressed in the examples do not represent the opinion of Merriam-Webster or its editors. Send us feedback.

See More

First Known Use of *leave*

Verb (1)

before the 12th century, in the meaning defined at transitive sense 1a(1)

Noun

before the 12th century, in the meaning defined at sense 1a

Verb (2)

14th century, in the meaning defined above

History and Etymology for *leave*

Verb (1)

Middle English *leven*, from Old English *lǣfan*; akin to Old High German ver*leiben* to leave, Old English be*līfan* to be left over, and perhaps to Lithuanian *lipti* to adhere, Greek *lipos* grease, fat

Noun

Middle English *leve*, from Old English *lēaf*; akin to Middle High German *loube* permission, Old English a*lȳfan* to allow — more at believe

Verb (2)

Middle English *leven*, from *leef* leaf

Keep scrolling for more

Learn More about *leave*

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Time Traveler for *leave*

The first known use of *leave* was before the 12th century

See more words from the same century

From the Editors at Merriam-Webster

Every Letter Is Silent, Sometimes

Every Letter Is Silent, Sometimes

When each letter can be seen but not heard

Dictionary Entries near *leave*

leathery turtle

Leathesia

leathwake

leave

leave a bad taste in someone's mouth

leave and license

leave at the altar

See More Nearby Entries

Phrases Related to *leave*

I must love you and leave you

beg leave

cause/create/leave a vacuum

come out of left field

compassionate leave

feel left out

have (got) nothing left to prove

Statistics for *leave*

Last Updated

16 Apr 2021

Look-up Popularity

Cite this Entry

"Leave." *Merriam-Webster.com Dictionary*, Merriam-Webster, https://www.merriam-webster.com/dictionary/leave. Accessed 28 Apr. 2021.

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MLA Chicago APA Merriam-Webster

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More Definitions for *leave*

leave

noun

English Language Learners Definition of *leave*

: a period of time when someone has special permission to be away from a job or from military service
formal **:** permission to do something

See the full definition for *leave* in the English Language Learners Dictionary

leave

verb
\ ˈlēv \
left\ ˈleft \; leaving

Kids Definition of *leave*

(Entry 1 of 2)

1 **:** to go away from Please *leave* the room.
2 **:** to cause to remain behind on purpose or without meaning to Oh, no, I *left* my mittens at school.*Leave* your money at home.
3 **:** to cause or allow to be or remain in a certain condition *Leave* the door open.
4 **:** to cause to remain as a trace, mark, or sign The cut *left* a scar.
5 **:** to have as a remainder Taking 7 from 10 *leaves* 3.
6 **:** to allow to be under another's control *Leave* everything to me.
7 **:** to cause to be available *Leave* room for dessert.
8 **:** to give by will She *left* property to the children.
9 **:** to give up He *left* school before graduating.
10 **:** deliver sense 1 She *left* the package on the way home.

leave

noun

Kids Definition of *leave* (Entry 2 of 2)

1 **:** permitted absence from duty or work The soldiers were off on *leave*.
2 **:** the act of going away and saying good-bye I had to take *leave* of a friend.
3 **:** permission I asked *leave* to speak.

leave

transitive verb
left; leaving

Legal Definition of *leave*

: bequeath, devise

Keep scrolling for more

More from Merriam-Webster on *leave*

Thesaurus: All synonyms and antonyms for *leave*

Nglish: Translation of *leave* for Spanish Speakers

Britannica English: Translation of *leave* for Arabic Speakers

Comments on *leave*

What made you want to look up *leave*? Please tell us where you read or heard it (including the quote, if possible).

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United States Court of Appeals for the Ninth Circuit

Office of the Clerk
95 Seventh Street
San Francisco, CA 94103

Information Regarding Judgment and Post-Judgment Proceedings

Judgment

- This Court has filed and entered the attached judgment in your case. Fed. R. App. P. 36. Please note the filed date on the attached decision because all of the dates described below run from that date, not from the date you receive this notice.

Mandate (Fed. R. App. P. 41; 9th Cir. R. 41-1 & -2)

- The mandate will issue 7 days after the expiration of the time for filing a petition for rehearing or 7 days from the denial of a petition for rehearing, unless the Court directs otherwise. To file a motion to stay the mandate, file it electronically via the appellate ECF system or, if you are a pro se litigant or an attorney with an exemption from using appellate ECF, file one original motion on paper.

Petition for Panel Rehearing (Fed. R. App. P. 40; 9th Cir. R. 40-1)
Petition for Rehearing En Banc (Fed. R. App. P. 35; 9th Cir. R. 35-1 to -3)

(1) A. Purpose (Panel Rehearing):

- A party should seek panel rehearing only if one or more of the following grounds exist:
  - ► A material point of fact or law was overlooked in the decision;
  - ► A change in the law occurred after the case was submitted which appears to have been overlooked by the panel; or
  - ► An apparent conflict with another decision of the Court was not addressed in the opinion.
- Do not file a petition for panel rehearing merely to reargue the case.

B. Purpose (Rehearing En Banc)

- A party should seek en banc rehearing only if one or more of the following grounds exist:

- ► Consideration by the full Court is necessary to secure or maintain uniformity of the Court's decisions; or
- ► The proceeding involves a question of exceptional importance; or
- ► The opinion directly conflicts with an existing opinion by another court of appeals or the Supreme Court and substantially affects a rule of national application in which there is an overriding need for national uniformity.

(2) Deadlines for Filing:

- A petition for rehearing may be filed within 14 days after entry of judgment. Fed. R. App. P. 40(a)(1).
- If the United States or an agency or officer thereof is a party in a civil case, the time for filing a petition for rehearing is 45 days after entry of judgment. Fed. R. App. P. 40(a)(1).
- If the mandate has issued, the petition for rehearing should be accompanied by a motion to recall the mandate.
- *See* Advisory Note to 9th Cir. R. 40-1 (petitions must be received on the due date).
- An order to publish a previously unpublished memorandum disposition extends the time to file a petition for rehearing to 14 days after the date of the order of publication or, in all civil cases in which the United States or an agency or officer thereof is a party, 45 days after the date of the order of publication. 9th Cir. R. 40-2.

(3) Statement of Counsel

- A petition should contain an introduction stating that, in counsel's judgment, one or more of the situations described in the "purpose" section above exist. The points to be raised must be stated clearly.

(4) Form & Number of Copies (9th Cir. R. 40-1; Fed. R. App. P. 32(c)(2))

- The petition shall not exceed 15 pages unless it complies with the alternative length limitations of 4,200 words or 390 lines of text.
- The petition must be accompanied by a copy of the panel's decision being challenged.
- An answer, when ordered by the Court, shall comply with the same length limitations as the petition.
- If a pro se litigant elects to file a form brief pursuant to Circuit Rule 28-1, a petition for panel rehearing or for rehearing en banc need not comply with Fed. R. App. P. 32.

- The petition or answer must be accompanied by a Certificate of Compliance found at Form 11, available on our website at www.ca9.uscourts.gov under *Forms.*
- You may file a petition electronically via the appellate ECF system. No paper copies are required unless the Court orders otherwise. If you are a pro se litigant or an attorney exempted from using the appellate ECF system, file one original petition on paper. No additional paper copies are required unless the Court orders otherwise.

Bill of Costs (Fed. R. App. P. 39, 9th Cir. R. 39-1)

- The Bill of Costs must be filed within 14 days after entry of judgment.
- See Form 10 for additional information, available on our website at www.ca9.uscourts.gov under *Forms.*

Attorneys Fees

- Ninth Circuit Rule 39-1 describes the content and due dates for attorneys fees applications.
- All relevant forms are available on our website at www.ca9.uscourts.gov under *Forms* or by telephoning (415) 355-7806.

Petition for a Writ of Certiorari

- Please refer to the Rules of the United States Supreme Court at www.supremecourt.gov

Counsel Listing in Published Opinions

- Please check counsel listing on the attached decision.
- If there are any errors in a published opinion, please send a letter **in writing within 10 days** to:
  - ► Thomson Reuters; 610 Opperman Drive; PO Box 64526; Eagan, MN 55123 (Attn: Jean Green, Senior Publications Coordinator);
  - ► and electronically file a copy of the letter via the appellate ECF system by using "File Correspondence to Court," or if you are an attorney exempted from using the appellate ECF system, mail the Court one copy of the letter.

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

Form 10. Bill of Costs

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9th Cir. Case Number(s)

Case Name

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