FINAL STATEMENT OF REASONS

TITLE 27, CALIFORNIA CODE OF REGULATIONS

SECTION 25805, SPECIFIC REGULATORY LEVELS: CHEMICALS CAUSING REPRODUCTIVE TOXICITY

MAXIMUM ALLOWABLE DOSE LEVELS FOR CHLORPYRIFOS (ORAL, INHALATION, AND DERMAL EXPOSURES)

This is the Final Statement of Reasons for the adoption of Maximum Allowable Dose Levels (MADLs) for oral, inhalation, and dermal exposures to chlorpyrifos. On May 24, 2019, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt proposed oral and inhalation MADLs for chlorpyrifos of 0.58 micrograms per day and a proposed dermal MADL for chlorpyrifos of 7.2 micrograms per day under Proposition 65[1] in Title 27, California Code of Regulations, section 25805(b)[2]. The Initial Statement of Reasons sets forth the grounds for the amendments to the regulation. A public comment period was provided from May 24, 2019 to July 8, 2019. The Notice stated that a public hearing would be held only on request. No request for a public hearing was received. OEHHA received written public comments on the proposed rulemaking from the following organizations:

1. Central California Asthma Collaborative (CCAC)
2. Dow AgroSciences LLC (DAS)

PEER REVIEW

OEHHA provided the Notice of Proposed Rulemaking and the Initial Statement of Reasons for the proposed MADLs for chlorpyrifos to the members of the Developmental and Reproductive Toxicant Identification Committee for their review and comment as required by Section 25801(f). No comments were received.

The OEHHA MADL is based on the same no observed effect level (0.01 mg/kg-day) for the same endpoint (developmental neurotoxicity) as adopted by the Department of Pesticide Regulation in its "Evaluation of Chlorpyrifos as an Air Toxic Contaminant"[3],

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 et seq., hereafter referred to as "Proposition 65" or "The Act".
[2] All subsequent citations are to Title 27, California Code of Regulations, unless otherwise noted.
[3] Available at: https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf

and scientifically peer reviewed by the Scientific Review Panel on Toxic Air Contaminants[4].

SUMMARY AND RESPONSE TO PUBLIC COMMENTS RECEIVED

In developing the MADLs for chlorpyrifos, OEHHA relied on the oral developmental toxicity study by Silva et al. (2017)[5] that reported neurobehavioral developmental effects of prenatal chlorpyrifos exposure in rat pups to establish the numeric basis for the MADLs, as well as analyses of absorption factors by the relevant routes of exposure in determining inhalation[6,7,8,9] and dermal[10,11,12] MADLs. The MADLs are based upon the results of the most sensitive scientific study deemed to be of sufficient quality[13]. OEHHA's responses to the comments received from the commenters listed above are incorporated within this Final Statement of Reasons (FSOR). Some of the comments submitted included observations or opinions on topics other than the actions proposed in this rulemaking, e.g., disagreeing with the listing of chlorpyrifos as causing reproductive toxicity (developmental endpoint). Accordingly, OEHHA is not required under the Administrative Procedure Act to respond to such comments in this FSOR. Because OEHHA is constrained by limitations upon its time and resources, and is not obligated by law to respond to irrelevant comments[14], OEHHA does not provide

[4] "Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting" available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf

[5] Silva JG, Boareto AC, Schreiber AK, Redivo DD, Gambeta E, Vergara F, Morais H, Zanoveli JM, Dalsenter PR. 2017. Chlorpyrifos induces anxiety-like behavior in offspring rats exposed during pregnancy. Neurosci Lett 641:94-100.

[6] Poet TS, Timchalk, C, Hotchkiss, JA, Bartels, MJ. 2014. Chlorpyrifos PBPK/PD model for multiple routes of exposure. Xenobiotica 44(10):868–881.

[7] Nolan, RJ, Dryzga, MD, Landenberger, BD, Kastl, PE. 1987. Chlorpyrifos: tissue distribution and metabolism of orally administered 14C-labeled chlorpyrifos in Fischer 344 rats. Dow Chemical Company, Midland, MI, Study # K-044793-(76) DPR Vol. 342-0343 # 071390, as cited in Department of Pesticide Regulation (DPR). 2018. Final Toxic Air Contaminant Evaluation of Chlorpyrifos. Risk Characterization of spray drift, dietary, and aggregate exposures to residential bystanders. July 2018. https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf

[8] DPR (2018). Final Toxic Air Contaminant Evaluation of Chlorpyrifos. Risk Characterization of spray drift, dietary, and aggregate exposures to residential bystanders. July, 2018. https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf [accessed November 7, 2018]

[9] Hotchkiss JA, Kriever SM, Brzak KA, Rick DL. 2010. Acute inhalation exposure of adult Crl:CD(SD) rats to particulate chlorpyrifos aerosols: Kinetics of concentration-dependent cholinesterase (ChE) inhibition in red blood cells, plasma, brain, and lung. Dow Chemical Company. Study #091133. CDPR record #258214, vol. #342-0908

[10] Griffin P, Mason H, Heywood K, Cocker J. 1999. Oral and dermal absorption of chlorpyrifos: a human volunteer study. Occup Environ Med 56(1):10-13.

[11] Nolan, R. J., Rick, D. L., Freshour, N. L., and Saunders, J. H. 1984. Chlorpyrifos: Pharmacokinetics in human volunteers following single oral and dermal doses. Toxicol. Appl. Pharmacol. 73: 8–15.

[12] Meuling WJA, Ravensberg LC, Roza L, van Hemmen JJ. 2005. Dermal absorption of chlorpyrifos in human volunteers. Int Arch Occup Environ Health 78:44-50.

[13] Section 25803(a)(5)

[14] California Government Code section 11346.9(a)(3)

responses to all of these remarks in this FSOR. However, the absence of responses to such remarks should not be construed to mean that OEHHA in any way agrees with them.

A summary of the public comments received that are relevant to this rulemaking is provided below, along with OEHHA's response to those comments. As explained in detail in the responses to comments, OEHHA declines to change the proposed MADLs based on the comments.

Comment 1 (DAS; pp. 7-8): "The DARTIC [Developmental and Reproductive Toxicant Identification Committee], through its opinion as "the state's qualified experts," concluded on November 29, 2017, that chlorpyrifos was "clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity." The developmental endpoint was not identified. Nonetheless, chlorpyrifos was added to the Proposition 65 list as a developmental toxicant on December 15, 2017."

"The challenge here is that the DARTIC did not identify a specific developmental effect as the basis for their decision to list chlorpyrifos under Proposition 65."

Response: On Nov. 29, 2017, the Developmental and Reproductive Toxicant Identification Committee (DARTIC) considered chlorpyrifos for listing under Proposition 65 as causing reproductive toxicity **based on the developmental toxicity endpoint**. The DARTIC considered evidence on the developmental toxicity of chlorpyrifos that included three review documents and more than 70 articles or reports published subsequent to these reviews[15]. This evidence included studies in humans, other mammals, and zebrafish, as well as *in vivo* and *in vitro* mechanistic studies, with several studies reporting neurodevelopmental effects. At the November 2017 meeting, the DARTIC found that chlorpyrifos has been clearly shown through scientifically valid testing according to generally accepted principles to cause developmental toxicity. In discussing the evidence for the developmental toxicity of chlorpyrifos from studies in humans, the DARTIC noted effects on general development, such as sudden infant death, as well as effects on neurodevelopment, including developmental delays in mental development, effects on motor development and intelligence, and attention disorders[16]. In discussing the evidence for the developmental toxicity of chlorpyrifos from studies in animals, the DARTIC highlighted a number of effects on

[15] Available at https://oehha.ca.gov/proposition-65/crnr/announcement-dartic-meeting-and-availability-hazard-identification-materials

[16] Transcript of the November 29, 2017 DARTIC meeting, pp. 21-22, 62-72, 144-148. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf

neurodevelopment and behavior including deficits in motor activity, spatial learning, and memory and increased anxiety-like behavior[17].

As stated in the Initial Statement of Reasons (ISOR) for this rulemaking[18], "(a)mong the affected endpoints of developmental toxicity caused by chlorpyrifos, neurobehavioral effects have been determined to be the most sensitive[19]. Of the several animal studies examining neurobehavioral developmental toxicity of chlorpyrifos, one critical study and three supportive study reports in laboratory animals provide relevant data for estimating the MADL".

Comment 2 (DAS; p. 3, 8): The commenter notes that Title 27, California Code of Regulations, section 25803(a)(1) states, "Only studies producing the reproductive effect which provides the basis for the determination that a chemical is known to the state to cause reproductive toxicity shall be utilized for the determination of the NOEL". The commenter cites this section of the regulations as support for the assertion that "studies utilized [as the basis for the MADL] must be able to show that the developmental effects were the result of pre-natal and not post-natal exposures."

Response: OEHHA notes that neither of the terms "pre-natal" or "post-natal" appear in Title 27, California Code of Regulations, Article 8. No Observable Effect Levels.

Section 25801(a) states:

> "The determination of whether a level of exposure to a chemical known to the state to cause reproductive toxicity has no observable effect for purposes of Section 25249.10(c) of the Act *shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of a chemical as known to the state to cause reproductive toxicity*. Nothing in this article shall preclude a person from using evidence, standards, assessment methodologies, principles, assumptions or levels not described in this article to establish that a level of exposure has no observable effect at one thousand (1000) times the level in question." (emphasis added)

[17] Transcript of the November 29, 2017 DARTIC meeting, pp. 25-42, 144-148. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf
[18] OEHHA (2019). Initial Statement of Reasons. Title 27, California Code of Regulations, Proposed Amendments to Section 25805(b), Specific Regulatory Levels: Chemicals Causing Reproductive Toxicity. Maximum Allowable Dose Levels for Chlorpyrifos (Oral, Inhalation, and Dermal Exposures). See p. 2. Available at https://oehha.ca.gov/media/downloads/crnr/chlorpyrifosisor052419.pdf
[19] Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting. Available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf.

The quantitative assessment and determination of the no observable effect level (NOEL) for chemicals listed as causing reproductive toxicity is discussed in Article 8, Section 25803. Assessment.

The beginning of Section 25803(a) states:

> "A quantitative assessment which conforms to this section shall be deemed to determine the level of exposure to a listed chemical which will have no observable effect, assuming the exposure at one thousand times the level in question. *The assessment shall be based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for listing the chemical as known to the state to cause reproductive toxicity*. In the absence of principles or assumptions scientifically more appropriate based upon the available data, the following default principles and assumptions shall apply in any such assessment:" (emphasis added)

Subsections 25803(a)(1) through 25803(a)(8) articulate a number of default principles and assumptions related to the determination of a NOEL.

Consistent with Sections 25801(a) and 25803(a), the proposed MADLs for chlorpyrifos are based on "evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing". As stated in the ISOR, "OEHHA identified the study in rats by Silva et al. (2017) as the most sensitive study deemed to be of sufficient quality, and thus it was selected as the basis for the oral MADL"[20]. Silva et al. (2017) was part of the hazard identification materials provided to the DARTIC for use in the committee's deliberations and subsequent decision to list chlorpyrifos as causing reproductive toxicity (developmental endpoint). Thus, Silva et al. (2017) is not just comparable to the evidence for listing, but is part of that evidence. The ISOR goes on to note that in the study by Silva et al. (2017)[21], chlorpyrifos exposures occurred during the prenatal period on gestation days (GDs) 14-20, and that doses of 0.1 milligrams per kilogram of bodyweight per day (mg/kg-day) and higher were found to increase anxiety and locomotor activity in male rat pups assessed on postnatal day (PND) 21.

The ISOR further notes that supportive studies include two studies where exposure of pregnant rats during GD 7-PND 21 to 0.1 mg/kg-day of chlorpyrifos resulted in decreased spatial learning in 2- to 3-month-old male pups[22] and increased locomotor

[20] OEHHA (2019), p. 4. Full citation provided in footnote 18.
[21] Silva et al. (2017), full citation provided in footnote 5.
[22] Gómez-Giménez B, Llansola M, Hernández-Rabaza V, et al. 2017. Sex-dependent effects of developmental exposure to different pesticides on spatial learning. The role of induced neuroinflammation in the hippocampus. Food Chem Toxicol 99:135-148.

activity in 2- to 3-month-old female pups[23], and a third study[24] in which exposure of pregnant rats during GD 6-PND 11 to 1 mg/kg-day resulted in decreased parietal cortex thickness in pups assessed on PND 66. Two of the supportive studies[25] were included in the hazard identification materials provided to the DARTIC, while the third study[26] was published after chlorpyrifos was placed on the Proposition 65 list.

Thus, derivation of the chlorpyrifos MADLs based on the NOEL from the study by Silva et al. (2017) is consistent with Sections 25801(a) and 25803(a) of the regulations.

Comment 3 (DAS; p. 4, 8): The commenter notes that Section 25803(a)(6) reads as follows: "The results obtained for the most sensitive study deemed to be of sufficient quality shall be applicable to all routes of exposure for which the results are relevant". The commenter cites this section of the regulations as support for the assertion that "three of the four studies, including the primary study cited by OEHHA, do not meet the regulatory definition "of sufficient quality" as required under the Statute (Cal. Health & Safety Code 25249.5 et seq.) and therefore should not serve as the bases for derivation of a MADL".

Response: The text of the statute does not include the words "sufficient" or "quality". However, OEHHA notes that Section 25249.10(c) of the statute states the following regarding levels of exposure to substances known to the state to cause cancer or reproductive toxicity:

> "An exposure for which the person responsible can show that the exposure poses no significant risk assuming lifetime exposure at the level in question for substances known to the state to cause cancer, and that the exposure will have no observable effect assuming exposure at one thousand (1000) times the level in question for substances known to the state to cause reproductive toxicity, *based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing of such chemical pursuant to subdivision (a) of Section 25249.8*. In any action brought to enforce Section 25249.6, the burden of showing that an exposure meets the criteria of this subdivision shall be on the defendant." (emphasis added)

[23] Gómez-Giménez B, Felipo V, Cabrera-Pastor A, Agusti A, Hernández-Rabaza V, Llansola M. 2018. Developmental exposure to pesticides alters motor activity and coordination in rats: Sex differences and underlying mechanisms. Neurotox Res 33(2):247-258.
[24] Hoberman AM. 1998a. Developmental neurotoxicity study of chlorpyrifos administered orally via gavage to Crl:CD®(SD)BR VAF/Plus® presumed pregnant rats. Argus Research Laboratories, Inc. Study # 304-001, Protocol # K-044793-109. DPR record #162521, vol. #342-746.
Hoberman A. 1998b. Supplement 1. Appendix M – Neuropathology Report: the adult rats (Day 66 postpartum). 23 Sep 1998.
[25] Gómez-Giménez et al. (2017), full citation provided in footnote 22. Hoberman (1998a, b), full citations provided in footnote 24.
[26] Gómez-Giménez et al. (2018), full citation provided in footnote 23.

As discussed in the response to Comment 2, the proposed MADLs for chlorpyrifos are based on "evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing". Specifically, the study in rats by Silva et al. (2017) was identified by OEHHA[27] as the most sensitive study deemed to be of sufficient quality, and was selected as the basis for the oral MADL[28]. This well-conducted study reported neurodevelopmental effects in offspring after exposure of pregnant Wistar rats during GD 14-20. More detailed responses to comments regarding issues of study quality for Silva et al. (2017) are presented below (see Comment 5).

The commenter also questions the quality of two of the three studies OEHHA identified as providing support for the development of the chlorpyrifos MADLs. These well-conducted studies exposed pregnant Wistar rats via diet to 0.1 mg/kg-day of chlorpyrifos during GD 7 - PND 21, and reported decreased spatial learning in the Morris water maze in their 2-3-month-old-male pups (Gómez-Giménez et al. 2017) and increased locomotor activity in their 2-3-month-old female pups (Gómez-Giménez et al. 2018). These observations were also supported by effects noted in an earlier study in which oral exposure of pregnant Sprague-Dawley rats during GD 6 - PND 11 to chlorpyrifos by gavage at 1 mg/kg-day resulted in decreased parietal cortex thickness in pups at PND 66 (Hoberman 1998a, b). More detailed responses to comments regarding issues of study quality for Gómez-Giménez et al. 2017 and Gómez-Giménez et al. 2018 are presented below (see Comment 6).

Comment 4 (DAS; pp. 4, 10-11): "Overall OEHHA's selection of one study and inclusion of three supportive studies is not reflective of the full toxicological database for chlorpyrifos and potential neurodevelopmental toxicity. A more complete evaluation of all relevant studies which meet the standards of the Regulation shows that chlorpyrifos does not cause neurodevelopmental effects at exposure levels below the current regulatory endpoint of Red Blood Cell Cholinesterase Inhibition (RBC ChEI)."

Response: As discussed in response to Comment 1, the DARTIC considered a large body of evidence on the developmental toxicity of chlorpyrifos, including three review documents and over 70 articles or reports published subsequent to those reviews[29]. This evidence included studies in humans, other mammals, and zebrafish, as well as *in vivo* and *in vitro* mechanistic studies, with several studies reporting neurodevelopmental effects. In contrast to the commenter's assertion that "chlorpyrifos does not cause neurodevelopmental effects at exposure levels below the current regulatory endpoint of Red Blood Cell Cholinesterase Inhibition (RBC ChEI)," neurodevelopmental effects of

[27] OEHHA (2019), p. 4. Full citation provided in footnote 18.
[28] Subsection 25803(a)(6)
[29] Available at https://oehha.ca.gov/proposition-65/crnr/announcement-dartic-meeting-and-availability-hazard-identification-materials

chlorpyrifos have been observed at low levels of exposure that are not associated with inhibition of brain acetylcholinesterase activity[30]. Indeed, California's Scientific Review Panel on Toxic Air Contaminants found that:

> "Chlorpyrifos exposure is associated with developmental neurotoxicological effects that have been documented in human epidemiology studies and in laboratory animal studies. Developmental neurotoxicity effects have been demonstrated to occur at levels substantially below the level that causes 10% inhibition of red blood cell (RBC) AChE, an endpoint that was used in previous assessments of Chlorpyrifos toxicity."[31]

In addition, the DARTIC, in discussing the evidence on the developmental toxicity of chlorpyrifos, stated, "the weight of the evidence supports that CPF [chlorpyrifos] is a developmental neurotoxicant, including at doses that do not or minimally suppress acetylcholinesterase activity in the brain"[32].

As stated in the ISOR under the heading STUDY SELECTION[33]:

> "Relevant studies that provide information on the developmental toxicity of chlorpyrifos were identified in the materials that formed the basis for listing chlorpyrifos as causing reproductive toxicity with the developmental endpoint[34]. A comprehensive literature search found one additional relevant study published since the Proposition 65 listing of chlorpyrifos[35]. All of the studies were reviewed and the most sensitive study deemed to be of sufficient quality was selected to provide the basis for the MADLs[36]."

Comment 5 (DAS; pp. 4-5, 10-12, 17): Silva et al. (2017) "does not meet the standard of "sufficient quality" and therefore cannot be used as the basis for a MADL for chlorpyrifos. The fundamental scientific limitations of this study include questions concerning the biological significance of the effect cited, the failure to measure red

[30] E.g., Levin ED, Addy N, Baruah A, Elias A, Christopher NC, Seidler FJ, Slotkin TA (2002) Prenatal chlorpyrifos exposure in rats causes persistent behavioral alterations, Neurotoxicol. Teratol. 24:733–741; Slotkin TA, Cooper EM, Stapleton HM, Seidler FJ (2013) Does thyroid disruption contribute to the developmental neurotoxicity of chlorpyrifos? Environ.Toxicol. Pharmacol. 36:284–287; Carr RL, Armstrong NH, Buchanan AT, Eells JB, Mohammed AN, Ross MK, Nail CA (2017) Decreased anxiety in juvenile rats following exposure to low levels of chlorpyrifos during development. Neurotoxicology 59:183-190.

[31] Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting. Available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf.

[32] Transcript of the November 29, 2017 DARTIC meeting, p. 42. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf

[33] OEHHA (2019), p. 2. Full citation provided in footnote 18.

[34] Available at https://oehha.ca.gov/proposition-65/crnr/announcement-dartic-meeting-and-availability-hazard-identification-materials

[35] Gómez-Giménez et al. (2018), full citation provided in footnote 23.

[36] Section 25803(a)(5)

blood cell cholinesterase inhibition (which is the regulatory endpoint), and the absence of a well-defined dose response, which is an accepted scientific principle for confirming a cause-and-effect relationship." Specifically:

a) "The investigators employed doses ranging from 0.01 to 10 mg/kg/day, but failed to report on purity of the test material or whether dose concentration verification was conducted."

b) "The group size ranged from 11 to 14 pregnant females per group. The actual number of offspring tested for behavioral effects on PND 21 and PND 70 is not stated. It is not clear whether testing included littermates, and if so, how the study controlled for the presence of littermates. Furthermore, it is not clear if animals were randomly assigned to dose groups."

c) The commenter states that in the Silva et al. (2017) paper, there was a lack of dose-response and the dose-spacing was quite wide (0.1-10.0 mg/kg for reported statistically significant observations), "which may infer that this endpoint (anxiogenic behavior) is not a particularly sensitive one. While locomotor activity was reported as statistically significant, the increased (relative to control) motor activity at 0.1 mg/kg/day was virtually the same as that reported following exposure to 10 mg/kg/day (i.e., no dose response for this observation)."

d) The commenter states that "while DAS is not asserting that cholinesterase inhibition represents the only or optimal point of departure, failure to measure it concomitantly in studies which are evaluating potential developmental toxicity should preclude any objective investigator from declaring that observed and reported developmental effects are or did occur below the threshold for cholinesterase inhibition. Silva et al. (2017) did not measure either brain or RBC ChEI."

e) The findings of Silva et al. (2017) are not consistent with five studies reviewed by Li et al. (2012) that also used the elevated plus maze to assess neurobehavioral effects of chlorpyrifos.

f) "Based on a review of the transcript of the DARTIC hearing, none of the Committee members identified or cited this study as a basis for listing even though it was available in the public, published literature well before the hearing."

Response:

a) Regarding the purity of the test material, Silva et al. (2017) specifically reported that the test substance used in the study and administered to the animals was purchased from Sigma-Aldrich and was "analytical standard" grade chlorpyrifos (Chemical

Abstract Service number 2921-88-2). Sigma-Aldrich[37] reports the purity of "analytical standard" grade chlorpyrifos as greater than or equal to 98%.

b) Regarding the assignment of animals (i.e., pregnant rats) to particular dose groups within the study, Silva et al. (2017) stated that "Pregnant females were randomly assigned into 5 groups of 11–14 each."

Regarding the allocation and number of pups tested in each dose group for specific behavioral effects at PND 21 and PND 70, the methods section of the paper states, "To evaluate the effects of CPF [chlorpyrifos] exposure on the offspring behavior, the male offsprings 1 (PND21) and 3 (PND70) were assessed by modified forced swimming test and open field test, while the offsprings 2 (PND21) and 4 (PND70) were assessed by the elevated plus-maze test (Fig. 1) in a number of 8-10 offspring per group." Figure 1 of the paper indicates that two groups of male pups were tested on PND 21 (testing group 1 in the modified forced swimming test and open field test, and testing group 2 in the elevated plus-maze test), and another two groups of male pups were tested on PND 70 (testing group 3 in the modified forced swimming test and open field test, and testing group 4 in the elevated plus-maze test). Furthermore, Table 2 indicates the number of pups per dose group (8, 10, 8, 10, and 8 in the control, 0.01, 0.1, 1, and 10 mg/kg-day groups, respectively) in testing groups 1 and 3. This information, taken together with the information presented in Table 1 of the paper (e.g., number of dams per dose group, total number of live births per dose group, male index of the litters of each dose group), indicates that there were sufficient numbers of male pups to avoid including littermates in a testing group. It is therefore reasonable to infer that the researchers allocated no more than one male pup per litter to each of the four testing groups, resulting in minimal influence of any one specific dam for each dose group.

c) As seen in Figure 4 and Table 2 from Silva et al. (2017), neurobehavioral effects were observed at doses of 0.1 mg/kg-day and above in male pups assessed on PND 21. Effects of prenatal chlorpyrifos exposure on anxiogenic behavior, measured as percentage of time spent in the open arms of the elevated plus-maze, in male pups at PND 21 were significantly different from the control group at the three highest doses tested (0.1, 1 and 10 mg/kg-day) (see Figure 4 of Silva et al. (2017)). This effect, i.e., decreased percentage of time spent in the open arms of the elevated plus maze, was consistently observed with prenatal exposure to chlorpyrifos at doses of 0.1 mg/kg-day and above in this study. Moreover, the magnitude of these decreases in percent time spent in the open arms of the maze is biologically significant. Prenatal chlorpyrifos exposure also affected locomotor activity, as measured in the open field test, in male pups at PND 21 at the three

[37] Available at https://www.sigmaaldrich.com/catalog/DataSheetPage.do?brandKey=SIAL&symbol=45395

highest doses tested (see Table 2 of Silva et al. (2017)). Statistically significant increases in locomotor activity were consistently observed with prenatal exposure to chlorpyrifos at doses of 0.1 mg/kg-day and above, and the magnitude of these increases, compared with control levels, is biologically significant. It is not known why the effect of prenatal chlorpyrifos exposure on these neurobehavioral parameters was not observed to increase as the dose was increased above 0.1 mg/kg-day. However, the absence of an observed dose-response with prenatal exposures to chlorpyrifos above 0.1 mg/kg-day does not change the fact that biologically and statistically significant effects were consistently observed with prenatal exposures of 0.1, 1 and 10 mg/kg-day in this study. No observable effect of chlorpyrifos treatment on either of these neurobehavioral measures was noted at 0.01 mg/kg-day, and thus this dose was identified as the NOEL.

d) As discussed above in the response to Comment 4, both the Scientific Review Panel on Toxic Air Contaminants[38] and the DARTIC[39] have stated that the neurodevelopmental effects of chlorpyrifos have been observed at doses that do not inhibit or minimally inhibit acetylcholinesterase activity in the brain. The fact that Silva et al. (2017) did not assess brain or RBC cholinesterase activity has no bearing on the validity of the study, or its findings of neurodevelopmental effects (i.e., increased anxiety and locomotor activity) in male pups exposed to chlorpyrifos during gestation.

e) The Li et al. (2012) article[40] reviewed five studies published prior to Silva et al. (2017) that also utilized the elevated plus maze to assess the neurobehavioral effects of prenatal exposure to chlorpyrifos. As summarized by the commenter, only one of the five elevated plus maze studies reviewed by Li et al. (2012) included a dose lower than 1.0 mg/kg-day, and Li et al. concluded that there were no consistent patterns of adverse effect in this assay at 1.0 mg/kg-day. In contrast, Silva et al. (2017) included two doses lower than 1.0 mg/kg-day, and, as discussed in response to Comment 5c above, observed a consistent pattern of increased anxiogenic behavior in the elevated plus maze at doses of 0.1, 1, or 10 mg/kg-day. The study by Silva et al. (2017) and the five elevated plus maze studies reviewed in Li et al. (2012) were each included in the hazard identification materials provided to the

[38] Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting. Available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf.

[39] Transcript of the November 29, 2017 DARTIC meeting, p. 42. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf

[40] Li AA, Lowe KA, McIntosh LJ, Mink PJ. 2012 Evaluation of epidemiology and animal data for risk assessment: Chlorpyrifos developmental and neurobehavioral outcomes. J Toxicol Env Health 15:109-184.

DARTIC as part of the evidence on the developmental toxicity of chlorpyrifos[41]. As stated in the ISOR, OEHHA identified the Silva et al. (2017) study, which measured clear effects on anxiety and locomotor activity on PND 21 in male pups following prenatal exposure to chlorpyrifos, as the most sensitive study deemed to be of sufficient quality for derivation of the chlorpyrifos MADLs.

f) As discussed in the response to Comment 1, the evidence on the developmental toxicity of chlorpyrifos provided to the DARTIC for their consideration was voluminous and included three review documents and over 70 articles or reports published subsequent to these reviews, including Silva et al. (2017)[42]. This evidence included studies in humans, other mammals, and zebrafish, as well as *in vivo* and *in vitro* mechanistic studies, with several studies reporting neurodevelopmental effects. In discussing the evidence for the developmental toxicity of chlorpyrifos from studies in animals, the DARTIC highlighted a number of effects on neurodevelopment and behavior including deficits in motor activity, spatial learning, memory and increased anxiety-like behavior[43]. That the committee did not specifically cite the Silva et al. (2017) study in their deliberations does not preclude its use in deriving the MADL.

As explained in the response to Comment 2, the proposed MADLs for chlorpyrifos are based on evidence and standards of comparable scientific validity to the evidence and standards which form the scientific basis for the listing. "OEHHA identified the study in rats by Silva et al. (2017) as the most sensitive study deemed to be of sufficient quality, and thus it was selected as the basis for the oral MADL"[44].

Comment 6 (DAS; pp. 5, 12-13, 17): The commenter states that OEHHA also lists two studies by Gomez-Gimenez (2017a, 2017b) as supportive of the proposed MADL, but these studies do not meet the standard of "sufficient quality" required in the regulation and therefore are unsuitable for determining a MADL for chlorpyrifos.

Specifically:

a) The two studies by Gomez-Gimenez (2017a, 2017b) involved both pre-and post-natal exposure. "One cannot determine if the effects reported were due to prenatal exposure vs. postnatal exposure, and the authors do not state otherwise."

[41] Available at https://oehha.ca.gov/proposition-65/crnr/announcement-dartic-meeting-and-availability-hazard-identification-materials
[42] *Ibid.*
[43] Transcript of the November 29, 2017 DARTIC meeting, pp. 25-42, 144-148. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf
[44] OEHHA (2019), p. 4. Full citation provided in footnote 18.

b) "Neither purity of the test substance nor dose level verification was noted as having been conducted," for either study.

c) Regarding the Gomez-Gimenez et al. (2017a) study, the commenter states that the "results were varied with some statistically significant effects reported, but in a scattered fashion where dose-responsiveness was rare and outcomes were gender-specific (i.e., reported decreased learning in males, but not females)."

d) Regarding the Gomez-Gimenez et al. (2017a) study, the commenter states that "it is not clear how the pups were prevented from ingesting the test material in the sweet jelly since the dams and pups were presumably housed together until weaning. No information was provided on the housing conditions of the animals."

e) Regarding the Gomez-Gimenez et al. (2017a) study, the commenter states that "the group size was small, with the offspring from only six dams per dose group used. The publication states, '[t]he litter effects were controlled by using pups from different litters per treatment group in each experiment.' However, the authors do not explain how this was done. The actual number of pups used per dose group, which were provided in Figure 1, ranged from 6 to 13 per dose. This means that some of the pups must have been littermates since there were only six dams per group. It is not clear how littermates were selected for testing. The authors do not state whether the litter or the pup was considered to be the statistical unit."

f) Regarding the Gomez-Gimenez et al. (2017a) study, the commenter states "[n]either brain nor RBC ChEI was measured."

g) Regarding the Gomez-Gimenez et al. (2017b) study, the commenter states there was "no dose-response observed", and the study had a small number of animals per group.

Response: As stated in the ISOR and as discussed in response to Comment 2, the study by Silva et al. (2017) served as the critical study to establish the numeric basis for the chlorpyrifos MADLs, while the studies by Gómez-Giménez et al. (2017) and Gómez-Giménez et al. (2018)[45] were identified as supportive studies that also provide data relevant for estimating the chlorpyrifos MADLs.

a) In the supportive studies by Gómez-Giménez et al. (2017) and Gómez-Giménez et al. (2018), pregnant rats were fed chlorpyrifos during GD 7 – PND 21. The first 10 days (PND 1-10) of rodent life are generally considered equivalent to weeks 23-40 of

[45] The commenter refers to these studies as Gómez-Giménez et al. (2017a) and Gómez-Giménez et al. (2017b).

gestation in humans, in terms of brain development (Semple et al. 2013)[46]. Therefore, exposure during the early postnatal period in rodents corresponds to the prenatal period of brain development in humans. While it is not possible to determine the extent to which chlorpyrifos exposures of nursing pups during PND 11 – 12 may have contributed to the neurodevelopmental effects reported in the studies of Gómez-Giménez et al. (2017) and Gómez-Giménez et al. (2018), the effects reported are consistent with and supportive of the findings of Silva et al. (2017)[47].

b) Regarding the purity of the test material, both Gómez-Giménez et al. (2017) and Gómez-Giménez et al. (2018) clearly state that the test substance used and administered to the animals was purchased from Sigma-Aldrich and was Chlorpyrifos PESTANAL®, 45395. This is "analytical standard" grade chlorpyrifos (Chemical Abstract Service number 2921-88-2). Sigma-Aldrich[48] reports the purity of "analytical standard" grade chlorpyrifos as greater than or equal to 98%.

In both studies chlorpyrifos was mixed in a sweet jelly, and dishes of the sweet jelly mixture were provided to the dams every afternoon during the dosing period. Neither paper indicated whether any analytical verification of chlorpyrifos doses was performed.

c) In the Gómez-Giménez et al. (2017) study, chlorpyrifos exposure during GD 7 – PND 21 resulted in statistically significant impairment of spatial learning (as measured in the Morris water maze) in male pups at all doses tested (0.1, 0.3, and 1 mg/kg-day). The magnitude of the effect was similar across the doses tested. It is not known why increasing doses of chlorpyrifos, ranging from 0.1 to 1 mg/kg-day, resulted in a similar, rather than an increasing magnitude of effect on spatial learning. Nevertheless, this study observed a consistent, statistically significant effect of chlorpyrifos on a specific behavioral endpoint in male pups relative to controls.

No effect of chlorpyrifos on spatial learning was observed in female pups. The gender specificity observed for this effect in this study is neither a cause for concern, nor a study limitation. Indeed, in discussing the evidence on the developmental toxicity of chlorpyrifos, the DARTIC commented on sexually dimorphic findings related to behavioral outcomes:

[46] Semple BD, Blomgren K, Gimlin K, Ferriero D, Noble-Haeusslein L. Brain development in rodents and humans: Identifying benchmarks of maturation and vulnerability to injury across species. Prog Neurobiol. 2013; 0: 1–16.
[47] Findings of Gómez-Giménez et al. (2018): increased locomotor activity observed at the lowest dose tested, 0.1 mg/kg-day. Findings of Gómez-Giménez et al. (2017): decreased spatial learning in Morris water maze observed at the lowest dose tested, 0.1 mg/kg-day.
[48] Available at https://www.sigmaaldrich.com/catalog/DataSheetPage.do?brandKey=SIAL&symbol=45395

"Other studies have also shown developmental exposure to rats and mice in different vehicles and routes of administration, produce spatial learning and memory deficits. And those deficits can, on occasion, be sexually dimorphic. That is that males and females respond differently, which suggests that there are specific challenges to understanding how mechanisms relate to behavioral outcomes."

d) In the Materials and Methods section, Gómez-Giménez et al. (2017) clearly indicates that chlorpyrifos was fed to the dams, and that care was taken to confirm that the dams consumed all the sweet jelly, and therefore all the dose of chlorpyrifos, stating:

"Pregnant Wistar rats (Charles River) were treated with pesticides or vehicle (corn oil, controls) from gestational day 7 to postnatal day 21. Pesticides were dissolved in corn oil and administered daily mixed in a sweet jelly (the volume of corn oil in the sweet jelly was between 50 and 200 µL every day. We confirmed that all rats eat all the sweet jelly and, therefore, all the dose of pesticide)."[49]

e) In the Materials and Methods section, Gómez-Giménez et al. (2017) states, "The offspring from 6 dams per group was used. Litter effects were controlled by using pups from different litters per treatment group in each experiment." Thus, it is evident that these researchers are cognizant of the need to control for possible litter effects, and took action to control for this. As shown in Figure 1A of the paper, the number of male pups tested per treatment group in the Morris water maze was 13, 6, 10, and 11, for the control, 0.1, 0.3, and 1 mg/kg-day chlorpyrifos treatment groups, respectively. Thus the information provided in the Materials and Methods section and Figure 1 indicates that approximately 2 pups per litter were tested in the Morris water maze from the control, 0.3, and 1 mg/kg-day chlorpyrifos treatment groups, and 1 pup per litter was tested from the 0.1 mg/kg-day chlorpyrifos treatment group.

In describing the statistical analysis of the data, Gómez-Giménez et al. (2017) do not indicate if the litter or the individual animal was considered the statistical unit. Given that the 2018 chlorpyrifos study from the same research group (i.e., Gómez-Giménez et al. 2018) states, "[t]he results are presented as the mean ± standard error of the mean (SEM), considering litter as statistical unit", it is reasonable to assume that the litter was also considered the statistical unit in the analyses presented in Gómez-Giménez et al. (2017).

[49] Gómez-Giménez et al. (2017), full citation provided in footnote 22.

f) As discussed above in the response to Comment 4, both the Scientific Review Panel on Toxic Air Contaminants[50] and the DARTIC[51] have stated that the neurodevelopmental effects of chlorpyrifos have been observed at doses that do not inhibit or minimally inhibit acetylcholinesterase activity in the brain. The fact that Gómez-Giménez et al. (2017) did not assess brain or RBC cholinesterase activity has no bearing on the validity of the study, or its findings that chlorpyrifos exposure during GD 7 – PND 21 resulted in statistically significant impairment of spatial learning in male pups at all doses tested (0.1, 0.3, and 1 mg/kg-day).

g) In the studies of Gómez-Giménez et al. (2018), locomotor activity was analyzed with the litter as the statistical unit. Locomotor activity was measured in male pups from 8 control dams and 4 chlorpyrifos exposed dams per dose group, and in female pups from 9 control dams and 4 chlorpyrifos exposed dams per dose group (See Gómez-Giménez et al. 2018, Figure 3). The statistical power to detect treatment-related effects at the p = 0.05 level was limited by the relatively small number of chlorpyrifos-exposed litters per dose group (n=4). Thus, the observations of statistically significant increases in locomotor activity in male and female pups in the 0.1 mg/kg-day dose groups, compared to controls, despite the limited statistical power, adds to the biological significance of the findings. No differences in locomotor activity were observed in pups of either sex in the 0.3 and 1 mg/kg-day dose groups. Gómez-Giménez et al. (2018) noted that "[loco]motor activity is modulated by complex interactions between glutamatergic, GABAergic, dopaminergic, and cholinergic systems involving different neuronal circuits and brain areas." Thus, the dose-related effects of chlorpyrifos on locomotor activity may be complex, with lower doses associated with predominately stimulatory effects associated with a subset of these neurotransmitter systems, and higher doses associated with no difference in activity compared to controls, due to a mix of effects on the different neurotransmitter systems.

Comment 7 (DAS; pp. 4-5, 13-17): "OEHHA cites the Developmental Neurotoxicity (DNT) study by Hoberman (1998) as the third study supportive of Silva et al. (2017). While this study does meet the standard of "sufficient quality," DAS disagrees with OEHHA's contention that the LOEL is 1 mg/kg/day based on parietal cortex morphometry in PND 66 rats. The study authors concluded the developmental NOEL was 1 mg/kg/day." (emphasis in original)

[50] Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting. Available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf.

[51] Transcript of the November 29, 2017 DARTIC meeting, p. 42. Available at: https://oehha.ca.gov/media/downloads/proposition-65/transcript/dartic112917meetingtranscript.pdf

"OEHHA failed to consider supplemental information and the full data record for this study. No historical DNT morphometric control data were available at the time this chlorpyrifos DNT study was conducted, but the lead researchers for the study conducted five DNT studies soon after the chlorpyrifos study, at the same laboratory and using the same methods, and issued Supplement 3, Historical Control Morphometric Data (Hoberman, 2000)."

"Small but statistically significantly differences in the thickness of the parietal cortex of high- and mid-dose female pups at two months of age were considered to be random effects and not treatment-related."

Response: In describing the study by Hoberman (1998a,b)[52] as supportive of the findings of Silva et al. (2017), Gómez-Giménez et al. (2017), and Gómez-Giménez et al. (2018), the ISOR states:

> "These observations were also supported by effects noted in an earlier study in which oral exposure of pregnant Sprague-Dawley rats during GD 6 – PND 11 to chlorpyrifos by gavage at 1 mg/kg-day resulted in decreased parietal cortex thickness in pups at PND 66 (Hoberman 1998a,b)[53]."

As summarized in Table 1 of the ISOR, the chlorpyrifos doses administered to the dams in the Hoberman (1998a,b) study were as follows: 0, 0.3, 1, and 5 mg/kg-day. OEHHA identified 1 mg/kg-day as the LOEL, based on decreased thickness of the parietal cortex, compared to controls, in pups at PND 66. The commenter also acknowledges that Hoberman (1998a,b) observed "[s]mall but statistically significant differences in the thickness of the parietal cortex of high- and mid-dose female pups at two months of age". OEHHA has determined that it is most appropriate to analyze the histopathological findings in Hoberman (1998a,b) using the study's concurrent controls, instead of comparing the findings to control data generated from five studies conducted subsequent to the Hoberman (1998a,b) study (referred to by the commenter as 'supplemental data'). This approach is also consistent with the US Environmental Protection Agency's Guidelines for Developmental Toxicity Risk Assessment[54] regarding control data which state:

> "Appropriate historical control data sometimes can be very useful in the interpretation of these endpoints. Comparison of data from treated animals with concurrent study controls should always take precedence over comparison with historical control data." (emphasis added)

[52] Hoberman (1998a, b). Full citations provided in footnote 24.
[53] *Ibid.*
[54] US EPA Guidelines for Developmental Toxicity Risk Assessment, Federal Register 56(234):63798-63826; December 5, 1991.

Comment 8 (DAS; p. 17): The commenter asserts that "[t]he 'most sensitive study of sufficient quality'" is the Hoberman et al. (1998) study, which OEHHA employed as one of the supporting studies in its proposed MADL."

"For purposes of establishing a MADL, comprehensive review of the studies used by OEHHA discussed above, indicates the most relevant, scientifically defensible NOEL from a study of 'sufficient quality' is 1 mg/kg/day derived from Maurissen et al (2000)" [the publication of the study conducted by Hoberman et al. (1998)].

Response: OEHHA disagrees with the commenter's statements that the "most sensitive study of sufficient quality" is the Hoberman et al. (1998) study and "the most relevant, scientifically defensible NOEL from a study of 'sufficient quality' is 1 mg/kg/day derived from Maurissen et al (2000) [Hoberman 1998a,b]", for the following reasons:

- First, as discussed in responses to Comments 3, 4, and 5, OEHHA considered the study design, study conduct, and study reporting of Silva et al. (2017), and finds it to be the most sensitive study of sufficient quality on the developmental toxicity of chlorpyrifos. Silva et al. (2017) measured clear effects on anxiety and locomotor activity on PND 21 in male pups following prenatal exposure to chlorpyrifos at doses of 0.1 mg/kg-day and higher, with 0.01 mg/kg-day identified as the study's NOEL.

- Second, as acknowledged by the commenter and discussed in response to Comment 7, statistically significant histopathological findings (i.e., decreases in the thickness of the parietal cortex) were observed in the study by Hoberman (1998a,b) at PND 66 in chlorpyrifos-exposed female pups in the high-dose (5 mg/kg/day) and mid-dose (1 mg/kg-day) groups. For the reasons discussed in the response to Comment 7, OEHHA disagrees with the commenter's contention that 1 mg/kg-day is the study NOEL, finding instead that it is the LOEL.

Comment 9 (DAS; pp. 5-6): "The [dermal absorption] value that OEHHA chose …. is not consistent with the Proposition 65 statute which stipulates the estimation of reasonably anticipated exposures, i.e., average exposure and dose values."

Response: The commenter's claim that "the Proposition 65 statute" "stipulates the estimation of reasonably anticipated exposures, i.e., average exposure and dose values" is not correct. The commenter incorrectly attributed language from Title 27, California Code of Regulations section 25821(c)(2) as being statutory.

Moreover, the regulatory language cited by the commenter is from Section 25821 Level of Exposure to Chemicals Causing Reproductive Toxicity, which pertains to estimation of the level of exposure to listed chemicals in consumer products by users of those

products. This section of the regulations (section 25821) is not relevant to the proposed regulatory action of adoption of Maximum Allowable Dose Levels (MADLs), since it pertains to exposure assessment (estimation of the level of exposure to listed chemicals) which plays no role in dose-response assessment (determination of the No Observable Effect Level and derivation of MADLs).

OEHHA further notes that Section 25803 provides guidance on quantitative dose-response assessment and derivation of MADLs.

Comment 10 (DAS; pp. 5-6, 19-23): "OEHHA's derivation of a dermal absorption value from one study is scientifically inappropriate and results in a dermal MADL that is incorrect and significantly over-estimates absorption." "OEHHA relied upon a single dermal absorption value (the highest) from one of the several studies that have been conducted." "The value OEHHA chose does not represent actual study data on absorption, nor does it represent the weight of evidence or the best science…"

The commenter disagrees with "the 9.6% value [for dermal absorption] that CDPR [California Department of Pesticide Regulation] has used", and suggests that an "[o]verall grand mean value of 2.5% dermal absorption, which is less than one-third of the 8% value used by OEHHA, can be estimated from all the available studies, and would reflect a reasonably anticipated exposure and absorbed dose for the average deposition used in the various studies."

The commenter states that this proposed "overall mean value" of 2.5% is further supported by physiologically-based pharmacokinetic and pharmacodynamics modeling (PBPK-PD) of chlorpyrifos for the dermal route of exposure", where the "estimated fractional absorption was 2.32% (Timchalk, et al. 2002)."

The commenter noted that the European Union (EU 2017) reviewed *in vivo* and *in vitro* dermal absorption studies conducted in rats and humans, and concluded that dermal absorption from a concentrated chlorpyrifos formulation (484 grams active substance/liter [g a.s./L]) was 0.9%,while dermal absorption from diluted chlorpyrifos solutions was greater (5% from a 1.80 g a.s./L solution and 7% from a 0.48 g a.s./L solution).

"The dermal absorption value selected is critical since it is the most sensitive variable in evaluating potential bystander exposure."

Response: OEHHA disagrees with the statements by the commenter that OEHHA's derivation of the dermal absorption factor for chlorpyrifos is scientifically inappropriate, that the value doesn't represent actual study data, and that the factor significantly overestimates absorption. As discussed in the ISOR, the dermal absorption factor of

8% used to derive the dermal MADL is based on a dermal pharmacokinetic study of chlorpyrifos conducted over a period of 120 hours in three human subjects, all of whom were adult males[55]. After taking into account the amount of chlorpyrifos that washed off the study subjects' skin four hours after application, the average dermal absorption of chlorpyrifos over the 120-hour study period among the study subjects is 8%. OEHHA finds that the results from this human dermal pharmacokinetic study are scientifically valid, as the study was well-designed, conducted, and reported. Thus, contrary to the statements made by the commenter, the dermal absorption factor OEHHA derived from this study is indeed scientifically appropriate, as it is based on actual study data collected over a period of 120 hours from three human subjects, and it is not an overestimate of absorption since it is based on the mean of the dermal absorption values observed for each of the subjects in the study.

OEHHA disagrees with the commenter's suggested approach of tabulating estimates of chlorpyrifos dermal absorption values from a number of different studies[56] employing a wide range of dermally applied chlorpyrifos doses, as well as different study designs, protocols, and methods, and then estimating "an overall grand mean value of 2.5% dermal absorption" from "all the available data". The commenter cites as support for this "overall grand mean value" of 2.5% a similar estimate for chlorpyrifos dermal absorption obtained with a physiologically based pharmacokinetic and pharmacodynamic model by Timchalk et al. (2002). However, the commenter also discussed additional values for chlorpyrifos dermal absorption that have been identified by other entities, which are generally more consistent with the value derived by OEHHA of 8% than with the DAS value of 2.5%. For example, the commenter noted that the California Department of Pesticide Regulation has used a dermal absorption value for chlorpyrifos of 9.6%, and that the European Union has concluded that dermal absorption values are greater when more dilute solutions of chlorpyrifos are used, with estimates of dermal absorption increasing from 5% to 7 % as chlorpyrifos concentrations decrease from 1.80 grams of active substance per liter [g a.s./L] to 0.48 g a.s./L. Thus, OEHHA has determined that the dermal absorption factor of 8%, which is based on the human dermal pharmacokinetic study conducted by Meuling et al. (2005)[57], is appropriate for use in deriving the dermal MADL for chlorpyrifos.

Finally, with regard to the commenter's statement that the dermal absorption value is the most sensitive variable in evaluating potential bystander exposure, OEHHA notes

[55] Meuling et al. 2005. Full citation provided in footnote 12.
[56] See Table 1 on page 21 of the comments submitted by DAS.
[57] Meuling et al. 2005, full citation provided in footnote 12.

that chlorpyrifos exposures to residential bystanders may occur via various scenarios[58], and involve multiple pathways, including inhalation, diet, and dermal contact.

Comment 11 (CCAC): The commenter states, "This toxic chemical has no proven safe level of exposure through to human being [*sic*] by any vector or route of administration. This conclusion is well supported and clearly proven by the existing studies referred to in the OEHHA document", citing the ISOR. The commenter notes that all four studies used to support the proposed "safe" exposure levels show effects following "short exposure cycles and follow-up periods", and states "[t]there is no literature on long term repeated exposure, no definitive literature on the impact of this chemical at lower dose on body systems not examined." The commenter points to references cited in the study of Silva et al. (2017) as support for concerns that chlorpyrifos may affect the liver and thyroid at much lower doses.

"[T]here is no established safe level there for [*sic*] the conclusion must be that no level is safe until proven otherwise. CCAC therefore recommends that OEHHA make a finding that a moratorium on the use of this "toxic chemical" be placed into effect immediately and/or within the term allowed under its authority."

Response: As discussed in the responses to Comments 1, 2, and 4, there is a large body of evidence on the developmental toxicity of chlorpyrifos, comprised of studies in humans, other mammals, and zebrafish, as well as numerous *in vivo* and *in vitro* mechanistic studies. Among the various endpoints of developmental toxicity caused by chlorpyrifos, it is the chemical's effects on the developing brain and neurobehavior that are most sensitive[59]. Of the several animal studies examining the neurobehavioral developmental toxicity of chlorpyrifos, OEHHA identified the study in rats by Silva et al. (2017) as the most sensitive study deemed to be of sufficient quality, and thus selected this study as the basis for the MADL.

In the study by Silva et al. (2017)[60], prenatal chlorpyrifos exposures on GD 14-20 at doses of 0.1 mg/kg-day and higher were found to increase anxiety and locomotor activity in male rat pups. No adverse effects were observed in pups exposed to 0.01 mg/kg-day chlorpyrifos, and thus 0.01 mg/kg-day was identified as the study NOEL. As described in the ISOR, the NOEL of 0.01 mg/kg-day provided by the study of Silva et al. (2017) was used as the basis for calculating the MADLs for chlorpyrifos. These

[58] DPR (2018). Final Toxic Air Contaminant Evaluation of Chlorpyrifos. Risk Characterization of spray drift, dietary, and aggregate exposures to residential bystanders. July 2018. https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_final_tac.pdf
[59] Findings of the Scientific Review Panel on the Proposed Identification of Chlorpyrifos as a Toxic Air Contaminant as adopted at the Panel's July 30, 2018 Meeting. Available at https://www.cdpr.ca.gov/docs/whs/pdf/chlorpyrifos_srp_findings.pdf.
[60] Silva et al. (2017), full citation provided in footnote 5.

calculations were performed in accordance with Section 25803 of the regulations, resulting in oral and inhalation MADLs for chlorpyrifos of 0.58 µg/day, and a dermal MADL for chlorpyrifos of 7.2 µg/day.

Further, OEHHA does not have the authority to institute a moratorium on the use of chlorpyrifos but notes that virtually all agricultural use of the pesticide chlorpyrifos in California will end by December 31, 2020[61].

ALTERNATIVES DETERMINATION

In accordance with Government Code section 11346.9(a)(4), OEHHA has, throughout the adoption process for this regulation, considered available alternatives to determine whether any alternative would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action. OEHHA has determined that no other reasonable alternatives suggested by the commenters to OEHHA or that have otherwise been identified or brought to the attention of OEHHA would either be more effective in carrying out the purpose for which the action is proposed, or would be as effective and less burdensome to affected private persons, or would be more cost effective to affected private persons and equally effective in implementing the statutory policy or other provision of law than the proposed regulation.

For chemicals listed under the Act as known to cause reproductive toxicity, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure will have no observable effect assuming exposure at one thousand (1,000) times the level in question for substances known to cause reproductive toxicity (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that will have no observable effect for reproductive toxicity.

The purpose of this regulation is to establish Maximum Allowable Dose Levels (MADLs) for chlorpyrifos. At or below these levels, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting these levels will allow businesses subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25249.6). Virtually all agricultural use of the pesticide chlorpyrifos in California will end by December 31, 2020[62], however, businesses may still be

[61] https://www.cdpr.ca.gov/docs/chlorpyrifos/index.htm
[62] https://www.cdpr.ca.gov/docs/chlorpyrifos/index.htm

required to provide warnings for residual chlorpyrifos on produce imported into California.

Although Section 25803 describes principles and assumptions for conducting quantitative assessments to derive MADLs, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting a MADL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

LOCAL MANDATE DETERMINATION

OEHHA has determined this regulatory action will not impose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.