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)

PURPOSE AND BACKGROUND OF PROPOSED AMENDMENTS

PURPOSE

The proposed regulatory amendments would adopt three Maximum Allowable Dose Levels (MADLs) for chlorpyrifos under Proposition 65[1] in Title 27, California Code of Regulations section 25805(b)[2]. The proposed MADLs were derived using scientific methods outlined in Section 25803. The proposed oral and inhalation MADLs are both 0.58 micrograms per day, and the proposed dermal MADL is 7.2 micrograms per day.

PROPOSITION 65 AND LISTING OF CHLORPYRIFOS

Proposition 65 was enacted as a ballot initiative on November 4, 1986. The Office of Environmental Health Hazard Assessment (OEHHA) within the California Environmental Protection Agency is the lead state entity responsible for the implementation of Proposition 65[3]. OEHHA has the authority to adopt and amend regulations to further the purposes of the Act[4].

The Act requires businesses to provide a warning when they cause an exposure to a chemical listed as known to the state to cause cancer or reproductive toxicity. The Act also prohibits the discharge of listed chemicals to sources of drinking water. Warnings are not required and the discharge prohibition does not apply when exposures are sufficiently small, as specified in the Act[5].

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[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] Health and Safety Code, section 25249.12 and Cal. Code of Regs., Title 27, section 25102(o).
[4] Health and Safety Code, section 25249.12(a).
[5] Health and Safety Code, section 25249.9(b) and 25249.10(c).

On December 15, 2017, chlorpyrifos was added to the Proposition 65 list as known to the state to cause reproductive toxicity (developmental endpoint), based on the findings of the state's qualified experts, the Developmental and Reproductive Toxicant Identification Committee (DARTIC)[6]. The DARTIC determined that chlorpyrifos had been clearly shown, through scientifically valid testing according to generally accepted principles, to cause developmental toxicity.

STUDY SELECTION

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[7]. A comprehensive literature search found one additional relevant study published since the Proposition 65 listing of chlorpyrifos[8]. 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[9]. The studies reviewed are described below.

Human Studies

No relevant human data for estimating the MADLs were identified in the materials that formed the basis for listing chlorpyrifos as causing reproductive toxicity, nor in a subsequent literature search by OEHHA.

Studies in Laboratory Animals

Among the affected endpoints of developmental toxicity caused by chlorpyrifos, neurobehavioral effects have been determined to be the most sensitive[10]. 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. In a study by Silva et al. (2017)[11], oral

[6] Health and Safety Code section 25249.8(b) and Section 25302 *et seq*.
[7] Available at https://oehha.ca.gov/proposition-65/crnr/announcement-dartic-meeting-and-availability-hazard-identification-materials.
[8] 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.
[9] Section 25803(a)(5).
[10] 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.
[11] 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.

exposure of pregnant Wistar rats during gestation days (GD) 14-20 to chlorpyrifos by gavage at 0.1 milligrams per kilogram of bodyweight per day (mg/kg-day) and higher doses were found to cause increased anxiety and increased locomotor activity in male rat pups on postnatal day (PND) 21. Supportive studies include two studies where dietary exposure of pregnant Wistar rats during GD 7- PND 21 to 0.1 mg/kg-day of chlorpyrifos in food (sweet jelly) resulted in decreased spatial learning in the Morris water maze in their 2-3-month-old-male pups (Gómez-Giménez et al. 2017)[12] and increased locomotor activity in their 2-3-month-old female pups (Gómez-Giménez et al. 2018)[13]. 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)[14]. No studies using other routes of exposure were identified.

Brief summaries of major findings on developmental toxicity in rats from these two oral gavage studies and two dietary exposure studies are presented in Table.1. All the studies identified were reviewed and considered by OEHHA for the establishment of the oral MADL.

[12] 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.
[13] Gómez-Giménez et al. (2018), full citation provided in footnote 8.
[14] 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.

Table 1. Key developmental neurotoxicity studies of chlorpyrifos

Study	Species Exposure Period, Route	Doses (mg/kg-day)[a]	POD (mg/kg-day)	Animals Tested and Key Effects
Critical Study				
Silva et al., 2017[15]	Rat dam GD 14 - 20 Gavage	0, 0.01, 0.1, 1, 10	0.01 (NOEL)	PND 21 male rat pups ↑ Anxiety ↑ locomotor activity
Supportive Studies				
Gómez-Giménez et al., 2017[16]	Rat dam GD 7 - PND 21 Food/diet	0, 0.1, 0.3, 1	0.1 (LOEL)	2-3-month-old male offspring ↓ Spatial learning in Morris water maze
Gómez-Giménez et al., 2018[17]	Rat dam GD 7 - PND 21 Food/diet	0, 0.1, 0.3, 1	0.1 (LOEL)	2-3-month-old male and female offspring ↑ Locomotor activity
Hoberman, 1998a,b[18]	Rat dam GD 6 - PND 11 Gavage	0, 0.3, 1, 5	1 (LOEL)	PND 66 pups ↓ parietal cortex thickness

[a] Chlorpyrifos was administered in corn oil via oral gavage in the studies by Silva et al. (2017) and Hoberman (1998a,b), and in corn oil mixed in a sweet jelly via diet in the studies by Gómez-Giménez et al. (2017; 2018).
Abbreviations: GD, gestation day; PND, postnatal day; NOEL, no observable effect level; LOEL, lowest observable effect level

STUDY SELECTED FOR MADL CALCULATIONS

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. The study provides a developmental no observable effect level (NOEL) of 0.01 mg/kg-day in Wistar rats. Developmental effects at the lowest observable effect level (LOEL) of 0.1 mg/kg-day in this study included increases in anxiety and locomotor activity, assessed on PND 21, in pups of dams exposed to chlorpyrifos *in utero* during GD 14-20. LOELs of 0.1 mg/kg-day were also identified in the two studies in rats by Gómez-Giménez et al. (2017, 2018) based on decreased spatial learning in the Morris

[15] Silva et al. (2017), full citation provided in footnote 11.
[16] Gómez-Giménez et al. (2017), full citation provided in footnote 11.
[17] Gómez-Giménez et al. (2018), full citation provided in footnote 8.
[18] Hoberman AM (1998a,b), full citation provided in footnote 14.

water maze in 2-3-month-old males and increased locomotor activity in 2-3-month-old females.

MADL CALCULATIONS

The following calculations were performed in accordance with Section 25803 to derive the MADLs for chlorpyrifos:

Oral exposure:

The Silva et al. (2017) study provided a NOEL of 0.01 mg/kg-day.

Calculation of the NOEL in mg/day for a 58 kilogram (kg) woman (Section 25803(b)):

0.01 mg/kg-day x 58 kg = 0.58 mg/day

The oral MADL is derived by dividing the oral NOEL expressed in mg/day by one thousand (Section 25801(b)(1)):

0.58 mg/day ÷ 1000 = 0.58 micrograms (µg)/day

$MADL_{oral}$ = 0.58 µg/day

Inhalation exposure:

Since there is no inhalation study of chlorpyrifos in pregnant animals, route-to-route extrapolation was used based on the results from the oral study by Silva et al. (2017). Inhalation pharmacokinetic studies of chlorpyrifos in the rat reported absorption rates of 72% for a 6-hour vapor exposure (Nolan et al. 1986, as cited by the California Department of Pesticide Regulation [DPR] 2018) and about 83% for a 6-hour dry particulate aerosol exposure (Hotchkiss et al. 2010). Since much of the particulate matter deposited in the lung is subsequently transported to the throat by muco-cilliary action and swallowed[19], and absorption by the oral route is 100%[20], OEHHA assumes that 100% of an inhaled aerosol of chlorpyrifos is ultimately absorbed. This is

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

[20] 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

consistent with the assumption used by other groups[21,22]. Thus, the inhalation MADL is also 0.58 µg/day.

$MADL_{inhalation}$ = 0.58 µg/day

Dermal exposure:

OEHHA determined a dermal absorption factor of 8% based on a dermal pharmacokinetic study of chlorpyrifos in the adult human by Meuling et al. (2005)[23]. In this study, application of approximately 5 mg chlorpyrifos (in ethanol) to approximately 100 square centimeters (cm^2) of the volar surface of the forearm (of 3 adult males) resulted in a mean absorption value of 4.3%, with a highest individual absorption value of 5.8%, as calculated from urinary excretion of the chlorpyrifos metabolite TCP (3,5,6-trichloro-pyridinol) over a 120-hour period. However, the authors reported that approximately 50% of the applied dose was washed off the skin with water 4 hours after application. When the potentially absorbed dose (the applied dose minus the washed-off dose) was used instead of the applied dose, the average dermal absorption was 7.9% (rounded to 8%) for this group. These findings are consistent with those of two other studies in humans (Nolan et al., 1984; Griffin et al., 1999)[24,25] that also reported slow and incomplete absorption of chlorpyrifos, in the range of approximately 1 to 5.8%. Since absorption by the oral route is 100%, the dermal MADL is calculated by multiplying the oral MADL by the reciprocal of the average dermal absorption value calculated from the study by Meuling et al. (2005) (i.e., 100/8).

Dermal MADL = Oral MADL × (100 ÷ 8)

0.58 µg/day × (100 ÷ 8) = 7.25 µg/day

$MADL_{dermal}$ = 7.2 µg/day (rounded to two significant figures)

[21] 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 [accessed November 7, 2018]

[22] 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.

[23] 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.

[24] 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.

[25] Nolan RJ, Rick DL, Freshour NL, Saunders JH. 1984. Chlorpyrifos: pharmacokinetics in human volunteers. Toxicol Appl Pharmacol 73:8-15.

Parties causing exposure to a listed chemical that exceeds the MADL are responsible for providing clear and reasonable warnings only for the exposures that they cause. If a party causes a knowing and intentional exposure to the chemical through multiple routes (e.g., expected airborne drift of an aerosolized chemical causing exposure by the inhalation, oral and dermal routes), the determination of whether a warning is required must be based on the cumulative exposure by all the relevant routes. Exposures to the same chemical from other sources for which the party in question is not responsible are not considered in making the determination of whether a warning is required[26].

Although route-specific MADLs for a chemical may differ because of differences in factors such as absorption and metabolism by different routes, the MADL for each route is a surrogate measure for an exposure level that will result in one thousandth of the highest internal dose at the site of action of the chemical that will cause no observable effect, irrespective of the external route of exposure. The exposure by each route should therefore be expressed as a percentage of the MADL for the route in question, then the percentages should be summed. If the total percentage is at or below 100% of the MADL, no warning is required.

PROPOSED REGULATORY AMENDMENTS

The proposed changes to Section 25805(b) are provided below in underline:

Chemical name	*Level (micrograms per day)*
Chlorpyrifos	0.58 (oral and inhalation)
Chlorpyrifos	7.2 (dermal)

PROBLEM BEING ADDRESSED BY THIS PROPOSED RULEMAKING

Proposition 65 does not provide guidance regarding how to determine whether a warning is required or a discharge is prohibited. OEHHA is the implementing agency for Proposition 65 and has the authority and expertise to examine the scientific literature and calculate a level of exposure, in this case a MADL, that does not require a warning or at which a discharge is not prohibited.

[26] Section 25821(a)

NECESSITY

These proposed regulatory amendments would adopt oral, inhalation and dermal MADLs that conform to the Proposition 65 implementing regulations and reflect the currently available scientific knowledge about chlorpyrifos. A MADL provides assurance to the regulated community that exposures or discharges at or below the level are considered not to pose a significant risk of developmental or reproductive harm. Exposures at or below the MADL are exempt from the warning and discharge requirements of Proposition 65[27].

BENEFITS OF THE PROPOSED REGULATION

See "Benefits of the Proposed Regulation" under **ECONOMIC IMPACT ANALYSIS** below.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDIES, REPORTS, OR DOCUMENTS

In determining the evidence and standards that formed the basis for listing chlorpyrifos under Proposition 65, OEHHA reviewed the scientific literature. These documents included numerous studies of the effects of chlorpyrifos, including *in vivo* studies in laboratory animals that provide evidence of developmental toxicity.

OEHHA relied on one study to establish the numeric basis for the MADLs:

1. 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.

OEHHA relied on analyses of absorption factors by the relevant routes of exposure in determining inhalation[28,29,30,31] and dermal[32,33,34] MADLs.

OEHHA also relied on the Economic Impact Analysis included below in developing this proposed regulation.

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[27] Health and Safety Code sections 25249.9(b) and 25249.10(c).
[28] Poet et al. (2014), full citation provided in footnote 19.
[29] Nolan et al. (1987), full citation provided in footnote 20.
[30] DPR (2018), full citation provided in footnote 21.
[31] Hotchkiss et al. (2010), full citation provided in footnote 22.
[32] Griffin et al. (1999), full citation provided in footnote 24.
[33] Nolan et al. (1984), full citation provided in footnote 25.
[34] Meuling et al. (2005), full citation provided in footnote 23.

REASONABLE ALTERNATIVES TO THE REGULATION AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES

MADLs provide "safe harbor" values that aid businesses in determining if they are required to provide a warning for a given exposure or prohibited from discharging a listed chemical. The alternative to the proposed amendments to Section 25805(b) would be to not promulgate MADLs for the chemical. Failure to promulgate these MADLs would leave the business community without a safe harbor level to assist businesses in complying with Proposition 65. No alternative that is less burdensome yet equally as effective in achieving the purposes of the regulation in a manner that achieves the purposes of the statute has been proposed.

REASONABLE ALTERNATIVES TO THE PROPOSED REGULATORY ACTION THAT WOULD LESSEN ANY ADVERSE IMPACT ON SMALL BUSINESSES

OEHHA is not aware of significant cost impacts that small businesses would incur in reasonable compliance with the proposed action. Use of the proposed MADLs by businesses is voluntary and therefore does not impose any costs on small businesses. In addition, Proposition 65 is limited by its terms to businesses with 10 or more employees (Health and Safety Code, section 25249.11(b)), so it has no effect on very small businesses.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT ADVERSE ECONOMIC IMPACT ON BUSINESS

Because the proposed MADLs provide "safe harbor" levels for businesses to use to comply with Proposition 65, OEHHA does not anticipate that the proposed regulation will have a significant statewide adverse economic impact directly affecting businesses, including the ability of California businesses to compete with businesses in other states.

EFFORTS TO AVOID UNNECESSARY DUPLICATION OR CONFLICTS WITH FEDERAL REGULATIONS CONTAINED IN THE CODE OF FEDERAL REGULATIONS

Proposition 65 is a California law that has no federal counterpart. There are no federal regulations addressing the same issues and, thus, there is no duplication or conflict with federal regulations.

ECONOMIC IMPACT ANALYSIS
Gov. Code section 11346.3(b)

It is not possible to quantify any monetary values for this proposed regulation because its use is voluntary and it only provides compliance assistance for businesses subject to the Act.

Creation, Elimination, or Expansion of Jobs/Businesses in California

This regulatory proposal will not affect the creation or elimination of jobs within the State of California. Proposition 65 requires businesses with ten or more employees to provide warnings when they expose people to chemicals that are known to cause cancer or developmental or reproductive harm. The law also prohibits the discharge of listed chemicals into sources of drinking water. Chlorpyrifos is listed under Proposition 65; this regulatory proposal identifies levels of exposures to chlorpyrifos that exempts businesses from the warning requirement and discharge prohibition.

Creation of New Businesses or Elimination of Existing Businesses within the State of California

This regulatory action will not impact the creation of new businesses or the elimination of existing businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides “safe harbor” values that aid businesses in determining if they are complying with the law with respect to chlorpyrifos exposures.

Expansion of Businesses within the State of California

This regulatory action will not impact the expansion of businesses within the State of California. The regulatory proposal does not create additional compliance requirements, but instead provides “safe harbor” values that aid businesses in determining if they are complying with the law with respect to chlorpyrifos exposures.

Benefits of the Proposed Regulation

The MADLs provide “safe harbor” values that aid businesses in determining if they are complying with the law. Some businesses may not be able to afford the expense of establishing a MADL and therefore may be exposed to litigation for a failure to warn or for a prohibited discharge of the listed chemical. Adopting this regulation will save these businesses those expenses and may reduce litigation costs. By providing safe harbor levels, this regulatory proposal does not require, but may encourage, businesses to lower the amount of the listed chemical in their product to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians.