M E M O R A N D U M

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DATE: February 7, 2024

SUBJECT: HUMAN HEALTH REFERENCE LEVEL REQUEST FOR CLOTHIANIDIN AND THIAMETHOXAM IN DRINKING WATER

On October 5, 2023, the Department of Pesticide Regulation's (DPR) Environmental Monitoring Branch (EMB) requested that the Human Health Assessment Branch (HHA) provide Human Health Reference Levels (HHRLs) for clothianidin and thiamethoxam for screening detections in groundwater and surface water to determine if they pose a risk to human health (Appendix 1). Clothianidin and thiamethoxam were detected in groundwater and surface water samples during routine screening conducted by the EMB Groundwater and Surface Water Protection Programs (GWPP and SWPP, respectively), which monitor for pesticides and related degradates with the potential to contaminate groundwater and/or surface water sources. Clothianidin and thiamethoxam were detected in 50.2% and 5.3% of surface water samples collected by DPR between 2019 and 2021, respectively, with maximum detected concentrations of 4.84 ppb for thiamethoxam and 0.13 ppb for clothianidin.

Conclusions and Recommendations:

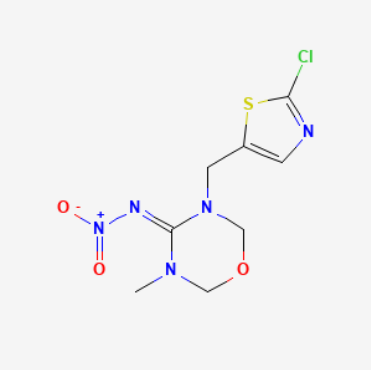
1. HHA calculated Human Health Reference Levels (HHRLs) to be used for detected or model-estimated residue levels of clothianidin and thiamethoxam in surface water using (1) acute and chronic consumption rates for drinking water from the National Health and Nutrition Examination Survey (NHANES) 2005–2010 database; and (2) toxicological endpoints established by the United States Environmental Protection Agency (US EPA).
2. DPR HHRLs for thiamethoxam and clothianidin at 120 and 980 parts-per-billion (ppb), respectively, apply to the evaluation of **maximum** residue level in drinking water and are

applicable for both surface water and groundwater sources. Thiamethoxam and clothianidin residue levels equal to or less than their corresponding DPR HHRLs are not expected to pose a risk to human health, including for sensitive subpopulations.

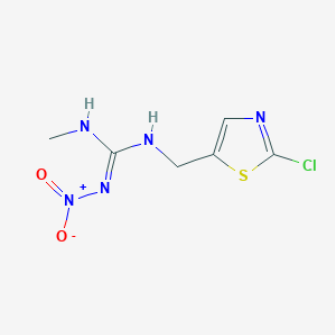
3. DPR Chronic Surface Water HHRLs at 24 and 196 ppb for thiamethoxam and clothianidin, respectively, apply to the evaluation of **average** residue levels in surface water. Average residue levels of thiamethoxam and clothianidin in surface water equal to or less than the DPR Chronic Surface Water HHRLs are not expected to pose a chronic risk to human health, including for sensitive subpopulations.

Background

Technical Name: Thiamethoxam
Chemical Name: (NE)-N-[3-[(2-chloro-1,3-thiazol-5-yl)methyl]-5-methyl-1,3,5-oxadiazinan-4-ylidene]nitramide
Chemical Abstracts Service Registry Number (CAS #): 153719-23-4
Molecular Weight: 291.71 g/mol (NIH, 2023a)
Chemical Structure:



Technical Name: Clothianidin
Chemical Name: 1-(2-Chloro-1,3-thiazol-5-ylmethyl)-3-methyl-2-nitroguanidine; (E)-N-[(2-Chloro-5-thiazolyl)methyl]-N'-methyl-N"-nitroguanidine
Chemical Abstracts Service Registry Number (CAS #): 210880-92-5
Molecular Weight: 249.68 g/mol (NIH, 2023b)
Chemical Structure:



Thiamethoxam is a broad spectrum nitroguanidine insecticide and part of the neonicotinoid class of pesticides. It is used against sucking and chewing insects such as leafhoppers or potato beetles on crops (USEPA, 2017b). Additionally, it is effective against interior and exterior pests such as termites and ants. The primary pesticidal mechanism of action is through interference of nicotinic acetylcholine receptors (nAChR); however, the specific receptor site is not known (USEPA, 2019b). Thiamethoxam was first registered by US EPA in 1999 (USEPA, 2020). As of January 2024, there were 28 active registrations in California (DPR, 2023d). According to the most recent available data from DPR's Pesticide Use Reporting (PUR) database, 33,367 pounds of thiamethoxam active ingredient were used in 24,115 California agricultural applications in 2021(DPR, 2021).

Clothianidin, a nitroguandine-substituted neonicotinoid insecticide, was first registered by US EPA in 2003. It is also the major metabolite of thiamethoxam (USEPA, 2009; USEPA, 2011a). As with the other neonicotinoid pesticides, clothianidin acts through nAChR. It is used to control a wide variety of pests including piercing, sucking and sporadic pests (USEPA, 2020). Additionally, it is the primary active ingredient in formulations for use on ornamentals, orchard and row crops, and for seed, soil, and turf treatments (USEPA, 2011a). As of January 2024, there were 36 active registrations in California (DPR, 2023d). According to the most recent available data from the DPR's Pesticide Use Reporting (PUR) database, 10,559 pounds of clothianidin active ingredient were used in 4,811 California agricultural applications in 2021(DPR, 2021).

A major biotransformation pathway of thiamethoxam is the cleavage of the oxadiazine ring to form the metabolite CGA0322704 (clothianidin) (USEPA, 2017b; USEPA, 2022). While thiamethoxam and clothianidin are independently registered as insecticides, tolerances for residues of thiamethoxam are established as combined residues of thiamethoxam and clothianidin, the latter expressed as a thiamethoxam equivalent (eCFR, 2023a). Tolerances for

residues of clothianidin are based only on clothianidin (eCFR, 2023b). Both pesticides were accounted for in the estimation of thiamethoxam residues in US EPA's food-only dietary exposure assessment. However, the agency evaluated residues of thiamethoxam and clothianidin separately in its drinking water evaluation (USEPA, 2017b; USEPA, 2019a; USEPA, 2020). A similar approach was used by HHA in developing the HHRLs. No other degradates of concern were identified for thiamethoxam or clothianidin in drinking water (USEPA, 2009; USEPA, 2019a; USEPA, 2022).

In 2021, US EPA determined that the weight of evidence supported a potential common mechanism among thiamethoxam, clothianidin and other neonicotinoid insecticides (acetamiprid, dinotefuran, imidacloprid, nithiazine and thiacloprid) and grouped them into a candidate common mechanism group (CMG) (USEPA, 2021c). The weight of evidence for a neonicotinoid CMG includes common structural features, agonism of the nAChR, and the induction of similar neurotoxic effects after acute exposure including reduced motor activity, decreased startle response, and clinical signs. US EPA used the PODs for these acute neurotoxic effects and the relative potency factor approach to conduct a screening-level cumulative acute dietary risk assessment which concluded that "cumulative risk estimates for neonicotinoids are below the levels of concern" and no further cumulative evaluation was necessary (USEPA, 2021c; eCFR, 2022). Because the neonicotinoids target different organs and systems following repeated exposures, US EPA determined that it would not be appropriate to form a candidate CMG based on repeated dose effects.

Review of Regulatory Documents and Databases

A review of pertinent regulatory documents was performed to ensure that the most scientifically supportable toxicological data were used for this evaluation (summarized in Table 1, below). A comprehensive systematic review was beyond the scope of the request.

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
DPR	2009	Guidance for Dietary Exposure Assessment	DPR, 2009
US EPA	2009	Clothianidin: Human Health Risk Assessment for Proposed Uses on Berries (Group 13-07H), Brassica Vegetables (Group 5), Cotton, Cucurbit Vegetables (Group 9), Fig, Fruiting Vegetables (Group 8), Leafy Green Vegetables (Group 4A), Peach, Pomegranate, Soybean, Tree Nuts (Group 14), and Tuberous and Corm Vegetables (Group 1C)	USEPA, 2009
US EPA	2010	Clothianidin - Human Health Risk Assessment of the Requested Experimental Use Permit as a Rice Seed Treatment	USEPA, 2010
US EPA	2011	Clothianidin. Human Health Assessment Scoping Document in Support of Registration Review.	USEPA, 2011a
US EPA	2011	Integrated Risk Information System (IRIS) Glossary.	USEPA, 2011b

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Regulatory Agency	Year	Title	Reference(s)
US EPA	2011	Thiamethoxam – Human Health Risk Assessment for Crop Group 15 (including buckwheat, pearl millet, proso millet, oats, rye, teosinte, triticale) and Crop Group 16 Commodities (forage, fodder, and stray of cereal grains group).	USEPA, 2011c
US EPA	2011	Thiamethoxam Summary Document Registration Review: Initial Docket	USEPA, 2011d
US EPA	2011	Thiamethoxam. Human Health Assessment Scoping Document in Support of Registration Review	USEPA, 2011e
US EPA	2012	Clothianidin – Human Health Risk Assessment for Requested Foliar Uses on Rice, Seed Treatment on Leafy Vegetables, Increased Application Rate for Vegetables, and Expanded Uses on Fruiting Vegetables and Pome Fruit.	USEPA, 2012
US EPA	2013	Thiamethoxam. Human Health Risk Assessment for the Higher Tolerance, Use of New Formulations, and Increased Maximum Seasonal Application Rate on Imported Coffee Beans, and Condition-of-Registration Data for Leafy Vegetables (Group 4).	USEPA, 2013
US EPA	2014	Dietary Exposure Evaluation Model User's Guide	USEPA, 2014
US EPA	2015	Human Health Ambient Water Quality Criteria: 2015 Update.	USEPA, 2015
US EPA	2017	Clothianidin - Drinking Water Exposure Assessment for Registration Review of All Registered Uses	USEPA, 2017a
US EPA	2017	Thiamethoxam: Draft Human Health Risk Assessment for Registration Review	USEPA, 2017b
US EPA	2018	2018 Edition of the Drinking Water Standards and Health Advisories Tables	USEPA, 2018a
US EPA	2018	Label Review Manual, Chapter 7: Precautionary Statements	USEPA, 2018b
USGS	2018	Health-Based Screening Levels for Evaluating Water-Quality Data	USGS, 2018
US EPA	2019	Clothianidin. Human Health Risk Assessment to Address Residues from New/Amended Uses of Thiamethoxam	USEPA, 2019a
US EPA	2019	Thiamethoxam. Human Health Risk Assessment for Adding Foliar Uses on Alfalfa, Certain Cereal Grains, and Potato, and a New Use on Sugarcane	USEPA, 2019b
US EPA	2020	Proposed Interim Registration Review Decision Case Numbers 7620 and 7614	USEPA, 2020
DPR	2021	2021 Annual Statewide Pesticide Use Report Chemical Totals	DPR, 2021
US EPA	2021	2021 Human Health Benchmarks for Pesticides	USEPA, 2021a
US EPA	2021	Human Health Benchmarks for Pesticides: Updated 2021 Technical Document	USEPA, 2021b
US EPA	2021	Neonicotinoid Cumulative Screening Analysis	USEPA, 2021c
DPR	2023	California Code of Regulations Title 3. Food and Agriculture Division 6. Pesticides and Pest Control Operations	DPR, 2023a
DPR	2023	California Pesticide Illness Query CalPIQ	DPR, 2023b
DPR	2023	Search for Chemical Ingredient by Partial Name, Chemical Code or CAS Number	DPR, 2023c

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
DPR	2023	Environmental Monitoring Programs and Projects	DPR, 2023d
eCFR	2022	40 CFR Part 180. Thiamethoxam; Pesticide Tolerances	eCFR, 2022
eCFR	2023	Code of Federal Regulation. § 180.565 Thiamethoxam; tolerances for residues.	eCFR, 2023a
eCFR	2023	Code of Federal Regulation. § 180.586 Clothianidin; tolerances for residues.	eCFR, 2023b
US EPA	2022	Thiamethoxam Human Health Risk Assessment for Use on Imported Pineapple. Office of Ground Water and Drinking Water.	USEPA, 2022
NIH	2023	PubChem Compound Summary for CID 86287519, Clothianidin	NIH, 2023b
NIH	2023	PubChem Compound Summary for CID 5821911, Thiamethoxam	NIH, 2023a
OEHHA	2023	The Proposition 65 List.	OEHHA, 2023
US EPA	2023	CompTox Chemicals Dashboard: Clothianidin	USEPA, 2023a
US EPA	2023	CompTox Chemicals Dashboard: Thiamethoxam	USEPA, 2023b
US EPA	2023	Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity	USEPA, 2023c
US EPA	2023	Human Health Water Quality Criteria and Methods for Toxics	USEPA, 2023d
US EPA	2023	Incident Data System (IDS) - Incidents Submitted in Aggregate	USEPA, 2023e
DPR: Department of Pesticide Regulation; eCFR: online version of Code of Federal Regulation; EFSA: European Food Safety Authority; US EPA: United States Environmental Protection Agency; USGS: United States Geological Survey; OEHHA: Office of Environmental Health Hazard Assessment			

Summary of Toxicology

Thiamethoxam has an acute Toxicity Category[a] value of III for oral and dermal hazards based on the median lethal doses and is classified as Toxicity Category IV for inhalation hazards based on its median lethal concentrations. It is not a skin sensitizer or a skin or eye irritant (Toxicity Category IV)(USEPA, 2017b). US EPA classified thiamethoxam as "not likely to be carcinogenic to humans" based on carcinogenicity studies in rats and mice (USEPA, 2017b).

Clothianidin has an acute Toxicity Category[b] value of III for oral and dermal hazards and Toxicity Category III for inhalation hazard based on median lethal doses and concentration. It is not a skin sensitizer nor a skin or eye irritant (Toxicity Category IV) (USEPA, 2017a). US EPA

[a] Acute Toxicity Categories. US EPA Label Review Manual Chapter 7: Precautionary Statements. US Environmental Protection Agency, Office of Pesticide Programs, Registration Division. Revised March 2018. Available at https://www.epa.gov/sites/default/files/2018-04/documents/chap-07-mar-2018.pdf USEPA. 2018b. Label Review Manual, Chapter 7: Precautionary Statements. https://www.epa.gov/sites/production/files/2018-04/documents/chap-07-mar-2018.pdf..

[b] Acute Toxicity Categories. US EPA Label Review Manual Chapter 7: Precautionary Statements. US Environmental Protection Agency, Office of Pesticide Programs, Registration Division. Revised March 2018. Available at https://www.epa.gov/sites/default/files/2018-04/documents/chap-07-mar-2018.pdf ibid..

classified clothianidin as "not likely to be carcinogenic to humans" based on carcinogenicity studies in rats and mice (USEPA, 2009).

Neither thiamethoxam nor clothianidin are included on the Proposition 65 (the California Safe Drinking Water and Toxic Enforcement Act of 1986) list for chemicals known to cause cancer, reproductive toxicity, or developmental toxicity (OEHHA, 2023).

Liver effects, changes in bodyweight, thyroid effects, and neurotoxicity are commonly observed following neonicotinoid exposure to in mammalian toxicity studies (USEPA, 2019a). For thiamethoxam, the main targets of toxicity are the liver, testes, adrenal glands, and hematopoietic system. Reported effects following repeated exposure include decreased body weight, tubular atrophy, changes to hematocrit, hemoglobin and erythrocytes, reduced thymus weight, and histopathological changes in the liver in rats and dogs (USEPA, 2017b; USEPA, 2022). For clothianidin, the main targets of toxicity are the liver, hematopoietic system, and kidneys. Neurotoxic effects reported after acute exposure in rats and mice included decreased spontaneous motor activity, tremors, deep respirations, and decrease reactivity (USEPA, 2009). Reported effects in developmental and reproductive toxicity studies included increased incidence of missing lobe of the lung in rabbits and decreased body weight gain and increased stillbirth in rats (USEPA, 2019a).

DPR's Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries reported in California from 1992 to 2018 (the most recent data available). There were 46 reported cases involving exposure to thiamethoxam in combination with other active ingredients and two cases for thiamethoxam alone. In these two cases, the individual experienced an itchy red rash with aches and redness to affected area (eye) (DPR, 2023b). There were four cases involving exposure to clothianidin in combination with other active ingredients; there were no cases for clothianidin alone. None of the 50 total reported cases involved co-exposure to thiamethoxam and clothianidin (DPR, 2023c).

HHA has evaluated all required toxicity data submitted as part of registration for thiamethoxam and clothianidin in California but has not conducted human health risk assessments for either pesticide. For purposes of this evaluation, HHA reviewed relevant regulatory documents (Table 1) and adopted toxicological endpoints and points of departure (PODs) established by US EPA for both thiamethoxam (USEPA, 2011c; USEPA, 2017b; USEPA, 2022) and clothianidin (USEPA, 2011a; USEPA, 2017a).

Thiamethoxam

US EPA's acute POD was a no observed adverse effect level (NOAEL) of 34.5 mg/kg/day based on decreased body weight and reduced brain morphometric measurements noted at the lowest observed adverse effect level (LOAEL) of 298.7 mg/kg/day in a developmental neurotoxicity study in rats (USEPA, 2011c; USEPA, 2017b; USEPA, 2022). The NOAEL was divided by a

total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose (aRfD[c]) of 0.35 mg/kg/day. The UF_{TOTAL} included 10x for interspecies extrapolation (UF_A) and 10x for intraspecies variation (UF_H) (USEPA, 2011c; USEPA, 2017b; USEPA, 2022). The chronic POD was a NOAEL of 1.2 mg/kg/day based on increased incidence and severity of tubular atrophy in F1 male testes observed at the LOAEL of 1.8 mg/kg/day in a two-generational reproductive study in rats (USEPA, 2011c; USEPA, 2017b; USEPA, 2022). The chronic RfD (cRfD) of 0.012 mg/kg/day was calculated by dividing the NOAEL by the UF_{TOTAL} of 100 as described above (USEPA, 2011c; USEPA, 2017b; USEPA, 2022).

Clothianidin

US EPA's acute POD was a NOAEL of 25 mg/kg/day based on transient decreased spontaneous motor activity, tremors, and deep respirations observed at the LOAEL of 50 mg/kg/day in an acute neurotoxicity study in mice (USEPA, 2009; USEPA, 2019a). This NOAEL was divided by a UF_{TOTAL} of 100 (see above) to calculate an aRfD of 0.25 mg/kg/day. (USEPA, 2009). The chronic POD was a NOAEL of 9.8 mg/kg/day based decreased body weight gains and delayed sexual maturation, decreased absolute thymus weights in F1 pups and increased stillbirths in both generations at the LOAEL of 31.2 mg/kg/day in a two-generational reproductive study in rats (USEPA, 2009). The chronic RfD of 0.098 mg/kg/day was calculated by dividing the NOAEL by the UF_{TOTAL} of 100 as described above (USEPA, 2009; USEPA, 2019a).

Calculation of Human Health Reference Levels

An HHRL is the threshold pesticide residue for a maximum water intake that results in the maximum safe oral exposure. HHRLs for thiamethoxam and clothianidin were calculated using their respective acute and chronic RfDs as the maximum safe exposure and the acute (95^{th} percentile) and chronic (mean) drinking water intake rates for non-nursing infants as the maximum water intake. Non-nursing infants were identified as having the highest consumption of drinking water per kilogram of bodyweight among the standard populations that HHA evaluates, including the general US population and other sensitive subpopulations such as children 1–2 years of age and women of childbearing age (13–49 years). The water consumption rates were extracted from the Dietary Exposure Evaluation Model - Food Commodity Intake Database (DEEM-FCID, version 4.02, 05-10-c) and the What We Eat in America (WWEIA) database. WWEIA is the dietary intake interview component of the National Health and Nutrition Examination Survey (NHANES). It is a collection of two-day dietary survey data (including drinking water consumption) from 2005 to 2010 for the US population and select subgroups (USEPA, 2014). HHA uses the 95^{th} percentile of the exposure levels for each population subgroup as the default upper bound for acute exposures, while two-day nonconsecutive food intake is used as a surrogate for chronic consumption patterns (DPR, 2009).

[c] An RfD is an estimate of a daily oral exposure for specific duration (acute or chronic) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Available at https://www.epa.gov/iris/iris-glossary USEPA 2011b. Integrated Risk Information System (IRIS) Glossary.

DPR Acute Human Health Reference Levels for Thiamethoxam and Clothianidin

DPR Acute HHRLs (commonly referred to as the DPR HHRLs) are for screening maximum pesticide residue levels in both surface water and groundwater and are applicable for single and repeat exposures. Maximum residue concentrations of thiamethoxam and clothianidin in drinking water equal to or less than their respective DPR HHRLs (**120** and **980** ppb, respectively; Table 2) are not expected to pose a risk to human health including for sensitive subpopulations.

DPR Chronic Surface Water Human Health Reference Levels for Thiamethoxam and Clothianidin

DPR Chronic Surface Water HHRLs are for screening average pesticide residue levels in a surface water body. Average residue concentrations of thiamethoxam and clothianidin in drinking water equal to or less than their respective DPR HHRLs (**24** and **196** ppb; Table 2) are not expected to pose a risk to human health including for sensitive subpopulations. DPR Chronic Surface Water HHRLs incorporate a relative source contribution (RSC) factor of 0.2. The RSC factor accounts for the possibility that exposure to a pesticide residue may come from sources other than drinking water (*i.e.*, food and air). A default RSC of 0.2 assumes that the exposure from water sources will be 20% of the total exposure while other intakes will make up the remainder (80%). This RSC factor is routinely used by regulatory agencies for deriving chronic screening levels of drinking water (USEPA, 2015; USEPA, 2023d). DPR Chronic Surface Water HHRLs that incorporate RSCs are only appropriate for the evaluation of averaged (*i.e.*, mean) residue levels in surface water.

Other Reference or Regulatory Levels for Thiamethoxam and Clothianidin in Drinking Water

DPR considers other reference and regulatory levels for drinking water in the development of HHRLs, especially with regards to best practices in dietary and drinking water exposure assessment. Common federal regulatory levels for drinking water include US EPA enforceable Maximum Contaminant Levels (MCLs[d]), non-legally enforceable Health Advisories (HAs[e]), and

[d] Maximum Contaminant Levels (MCLs) are used for the protection of public drinking water systems and do not apply to privately owned wells or any other individual water system. Available at https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf USEPA. 2018a. 2018 Edition of the Drinking Water Standards and Health Advisories Tables.

[e] Health Advisories (HAs) are estimated acceptable drinking water levels for chemicals based on information of adverse health effects and are not legally enforceable Federal standards, but rather serve as technical references to be used by federal, state, and local officials. Available at https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf

Human Health Benchmark for Pesticides (HHBP[f]), and United States Geological Survey (USGS) Health-Based Screening Levels (HBSLs[g]) (USEPA, 2018a; USGS, 2018; USEPA, 2021b). For thiamethoxam and clothianidin, US EPA issued chronic Human Health Benchmark for Pesticides (HHBP) of 71 and 580 ppb, respectively, for the general population (USEPA, 2021b; USEPA, 2021a). Although the same chronic PODs were used to derive the HHBP and DPR HHRLs, the US EPA chronic HHBP and DPR HHRLs differ because they were calculated using a different water consumption rate.

[f] The 2021 US EPA Human Health Benchmark for Pesticides (HHBPs) contain 430 pesticides that currently have no federal drinking water standards. HHBPs are not legally enforceable, but rather are provided by US EPA for pesticides that have no drinking water standards or health advisory (HA). Available at https://www.epa.gov/system/files/documents/2021-07/hh-benchmarks-technical-document-2021.pdf USEPA 2021b. Human Health Benchmarks for Pesticides: Updated 2021 Technical Document. Office of Ground Water and Drinking Water, United States Environmental Protection Agency.

[g] USGS Health-Based Screening Levels (HBSLs) are "non-enforceable water-quality benchmarks" that were developed using (1) the latest US EPA Office of Water methods for establishing drinking-water guidelines and (2) the most recent US EPA peer-reviewed publicly available toxicity information. Available at https://water.usgs.gov/water-resources/hbsl/USGS. 2018. Health-Based Screening Levels for Evaluating Water-Quality Data. United States Geological Survey.

Table 2. DPR HHRLs[a] for Thiamethoxam and Clothianidine

Residue	Acute or Chronic	Water Consumption Rates for Non-Nursing Infants[b] (L water/kg BW)	RfD[c] (mg/kg/day)	HHRL (ppb)	US EPA Chronic HHBP[d] (ppb)
Thiamethoxam	Maximum Residues (Acute)[e]	0.10	0.012	**120**	71 (General Population)
	Average Residues (Chronic Surface Water)	0.10	0.012	**24**	
Clothianidin	Maximum Residues (Acute)[e]	0.10	0.098	**980**	580 (General Population)
	Average Residues (Chronic Surface Water)	0.10	0.098	**196**	

BW: bodyweight; DPR: Department of Pesticide Regulation; HHBP: Human Health Benchmark for Pesticides; HHRL: Human Health Reference Level; L: liter; NA: not applicable; RfD: reference dose; ppb: parts-per-billion.

[a] The DPR HHRLs are calculated for screening maximum pesticide residue levels (DPR Acute HHRLs) or for screening average pesticide residue levels (DPR Chronic Water HHRLs) in a water body. DPR Acute HHRLs (ppb) = [RfD (mg/kg/day) x 1000] / [daily water intake]; DPR Chronic HHRLs in surface water = [chronic RfD (mg/kg/day) x 1000 x RSC] / [chronic daily water intake]. Daily water intake is 95th percentile for acute or chronic (mean) water consumption rates for non-nursing infants (see Note b); RSC: relative source contribution, assumed as 20% (USEPA, 2015).

[b] 95th percentile water consumption rates for non-nursing infants were from NHANES database (2005–2010). Acute and chronic water consumption data were extracted using the Dietary Exposure Evaluation Model - Food Commodity Intake Database (DEEM-FCID, version 4.02, 05-10-c). A residue level of 1 ppm consumption defaults to the consumption rates by dimensional analysis (acute = 0.194566 L water/kg BW and chronic = 0.099559 L water/kg BW). The values were rounded to two decimal points for the calculation of HHRLs.

[c] Acute and chronic RfDs for thiamethoxam and clothianidin were based on toxicological endpoints established by US EPA as described in the text (USEPA, 2009; USEPA, 2011c; USEPA, 2011a; USEPA, 2017a; USEPA, 2022).

[d] In 2021, US EPA provided Human Health Benchmark for Pesticides (HHBPs) containing 430 pesticides that currently have no federal drinking water standards. HHBPs are not legally enforceable, but rather are provided by US EPA for pesticides that have no drinking water standards or health advisories(USEPA, 2021b). A Chronic HHBP for General Population (ppb) = [chronic RfD (mg/kg/day) x 1000 x 0.2 RSC] / 0.0338 (L/kg/day) DWI-BW ratio. DWI: daily water intakes.

[e] A DPR Acute HHRL (ppb) was the lower value of the following two calculations for thiamethoxam: [acute RfD (mg/kg/day) x 1000] / [acute daily water intake] = 0.345*1000 / 0.19 = 1,816; and [chronic RfD (mg/kg/day) x 1000] / [chronic daily water intake] = 0.012*1000 / 0.10 = 120; and for clothianidin: acute RfD (mg/kg/day) x 1000] / [acute daily water intake] = 0.25*1000 / 0.19 = 1,316; and [chronic RfD (mg/kg/day) x 1000] / [chronic daily water intake] = 0.098*1000 / 0.10 = 980.

The recommended HHRLs for screening thiamethoxam and clothianidin residues in drinking water are **bolded**.

Conclusions

HHA calculated Human Health Reference Levels (HHRLs) to be used for thiamethoxam and clothianidin in drinking water. Maximum residue concentrations of thiamethoxam and clothianidin equal to or less than the DPR HHRL in drinking water (120 or 980 ppb, respectively), or average residue concentrations in surface water equal to or less than the DPR Chronic Surface Water HHRL (24 or 196 ppb, respectively) are not expected to pose a risk to human health, including for sensitive subpopulations.

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Appendix 1: DPR Memo: Human Health Reference Level Request For Clothianidin and Thiamethoxam in Drinking Water (October 5, 2023) (1 page)

Department of Pesticide Regulation

Julie Henderson
Director

Gavin Newsom
Governor

Yana Garcia
Secretary for Environmental Protection

MEMORANDUM

TO: Shelley DuTeaux
Environmental Program Manager II
Human Health Assessment Branch

VIA: Minh Pham — *Original Signed by 10/5/23*
Environmental Program Manager II
Environmental Monitoring Branch

FROM: Joy Dias — *Original Signed by 10/5/23*
Environmental Program Manager I
Environmental Monitoring Branch

Anson Main, Ph.D. — *Original Signed by 10/5/23*
Environmental Program Manager I
Environmental Monitoring Branch

DATE: October 5, 2023

SUBJECT: HUMAN HEALTH REFERENCE LEVEL REQUEST FOR CLOTHIANIDIN AND THIAMETHOXAM IN DRINKING WATER

The Environmental Monitoring Branch (EMB) monitors the environment to determine the fate of pesticides and protects the public and the environment from pesticide contamination by analyzing hazards and developing pollution prevention strategies. Consistent with EMB's mission, the Groundwater Protection Program (GWPP) and the Surface Water Protection Program (SWPP) monitor for pesticides and degradates with the potential to contaminate groundwater and surface water in the State.

During routine monitoring with updated analytical methods that include clothianidin and thiamethoxam, the GWPP recently detected clothianidin in groundwater samples. Clothianidin is both an active ingredient (AI) and a degradate of the AI thiamethoxam. SWPP has monitored for clothianidin and thiamethoxam in California's agricultural regions since 2019. In a review of SWPP monitoring data from 2019 to 2021, 50.2% of samples collected contained thiamethoxam and 5.3% contained clothianidin. To date, the highest concentrations detected in surface water were 4.84 ppb (thiamethoxam) and 0.13 ppb (clothianidin).

To determine whether detections of clothianidin or thiamethoxam pose a significant risk to human health, EMB requests that the Human Health Assessment Branch provide human health reference levels to use for screening detections in groundwater and surface water.

cc: Carissa Ganapathy, Senior Environmental Scientist (Supervisory)
Xin Deng, Ph.D., Senior Environmental Scientist (Supervisory)