



Department of Pesticide Regulation



Brian R. Leahy
Director

MEMORANDUM

Edmund G. Brown Jr.
Governor

TO: Pam Wofford, Chief
Environmental Monitoring Branch

VIA: Shelley DuTeaux, PhD MPH, Chief
Human Health Assessment Branch

FROM: Pete Lohstroh, PhD, Staff Toxicologist [original signed by P. Lohstroh]
Svetlana Koshlukova, PhD, Senior Toxicologist [original signed by S. Koshlukova]
Risk Assessment Section
Human Health Assessment Branch

DATE: April 10, 2018

SUBJECT: EVALUATION OF THE POTENTIAL HUMAN HEALTH EFFECTS FROM DRINKING WELL WATER CONTAINING IMIDACLOPRID

On January 11, 2018, the Department of Pesticide Regulation (DPR), Human Health Assessment (HHA) Branch was notified by the Environmental Monitoring Branch that imidacloprid was detected in the water of 14 wells. The detected levels of ranged from 0.054 to 5.97 parts-per-billion (ppb) with an analytical reporting limit (RL) of 0.05 ppb. The DPR Environmental Monitoring Branch requested that HHA determine whether or not there is a health concern for individuals using these wells as a source of drinking water. This memo is in response to that request.

Conclusions and Recommendations:

1. The human health risk to the maximum level of imidacloprid measured in well water was evaluated by acute and chronic drinking water exposure analyses using toxicological endpoints established by DPR and estimates for the consumption of drinking water based on the National Health and Nutrition Examination Survey (NHANES) 2005-2010 database. Exposures were evaluated for the US population and for subgroups with the potential for enhanced sensitivity, including infants, children, and women of childbearing age.
2. Our results indicate that imidacloprid concentrations of 5.97 ppb in California well water do not pose acute or chronic health concerns.
3. Based on our assessment, we recommend that imidacloprid detections in California wells be compared to a reference level of 283 ppb. Detected residues higher than this level may pose a health concern and should be sent to HHA for further evaluation.

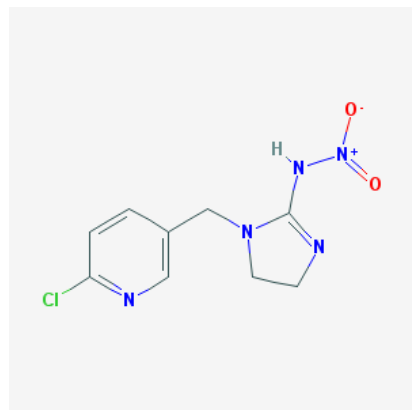


Background

Technical Name: Imidacloprid

Chemical name: N-[1-[(6-chloropyridin-3-yl)methyl]-4,5-dihydroimidazol-2-yl]nitramide;
Chemical Abstracts Service Registry Number (CAS) 138261-41-3 (NIH, 2018)

Chemical Structure:



Reference: (NIH, 2018)

Imidacloprid is a neurotoxic insecticide that belongs to the class of the neonicotinoid pesticides. The toxicity of imidacloprid is largely due to interference of the neurotransmission in the nicotinic cholinergic nervous system (DPR, 2006). Prolonged exposure to of imidacloprid may cause incoordination, tremors, decreased activity, reduced body temperature, and at very high doses death. Imidacloprid is a Category II (moderate) acute toxicant based on its median oral dose in mice (LD₅₀) and thus, is classified as a General Use Pesticide (DPR, 2006). In acute, subchronic and chronic studies in rats, mice and dogs the primary target organs of imidacloprid toxicity were the nervous system, liver, and thyroid gland (DPR, 2006). Imidacloprid is not classified as a carcinogen by USEPA. In their cancer classification, imidacloprid is designated as a Group E chemical showing evidence of non-carcinogenicity for humans (USEPA, 2010).

DPR considers imidacloprid to have potential as a groundwater contaminant based on its physicochemical properties. In well water, imidacloprid is expected to slowly degrade by hydrolysis (DPR, 2006). The rate of hydrolysis is increased with increasing alkalinity with an estimated half-life of 355 days when water pH = 9 (DPR, 2006).

Summary of Toxicology

A DPR risk characterization document (RCD) for imidacloprid was issued in 2006 that included evaluations of dietary and drinking water risks (DPR, 2006). An acute no-observed-effects-level

(NOEL) of 9.0 mg/kg/day was established based on decreased motor activity in adult rats. This NOEL was used to estimate the risk for acute dietary exposure to imidacloprid to the general population. A NOEL of 5.5 mg/kg/day for developmental neurotoxicity (DNT) was established based on significant decreases in the dimensions of brain structures in young rats (postnatal day 11 pups) after 32 doses to the dams during the periods of gestation and lactation. The NOEL for the DNT study was used to evaluate acute exposures to imidacloprid in women of childbearing age, infants and children. This NOEL is also applicable for repeated (subchronic or chronic) exposures to imidacloprid. It is similar to the chronic NOEL of 5.7 mg/kg/day based on toxicity to the thyroid gland in chronic studies using adult rats. The NOEL of 5.5 for DNT effects in rats was used for evaluation of both acute and chronic analyses described in this memo.

In 2017, US EPA Office of Ground Water and Drinking Water established acute and chronic human health benchmarks for pesticides (HHBPs) for imidacloprid (USEPA, 2017c). The acute HHBP (930 ppb) that was based on an acute population adjusted dose (aPAD) of 0.14 mg/kg/day based on a lowest-observed-adverse-effects-level (LOAEL) of 42 mg/kg/day from an acute neurotoxicity study using rats and a total uncertainty factor (UF) of 300 (USEPA, 2010; USEPA, 2017b; USEPA, 2017c). An aPAD or an acute reference doses (aRfD) is defined as “an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for an acute duration (24 hours or less) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime (USEPA, 2011).”

A chronic HHBP (360 ppb) was also established based on a chronic population adjusted dose (cPAD) of 0.057 mg/kg/day based on a no-observed-adverse-effects-level (NOAEL) of 5.7 mg/kg/day from a chronic toxicity study using rats and a total uncertainty factor (UF) of 100 (USEPA, 2010; USEPA, 2017b). The PAD is considered to be the maximum, safe, exposure level. Per US EPA (USEPA, 2017a) (pg. 1): “HHBPs are levels of certain food use pesticides in water at or below which adverse health effects are not anticipated from one-day or lifetime exposures.” Further, “EPA is providing the HHBPs for informational purposes for use by states, water systems and the public to help understand monitoring data for pesticides that have no drinking water standards or health advisories. Drinking water systems can also use them as reference values to respond to customer inquiries if pesticides are detected through monitoring.”

Evaluation of the Imidacloprid Residue

Drinking Water Exposure Analysis

We estimated the acute and chronic exposures to imidacloprid in drinking water using the Dietary Exposure Evaluation Model - Food Commodity Intake Database (DEEM-FCID, version 4.02, 5-10c) and the NHANES/“What We Eat in America” (WWEIA). The NHANES/WWEIA is a collection of two-day dietary survey data from 2005 to 2010 for the US population and select subgroups. The 95th percentile exposures were used for the acute analysis, while 2-day average exposures were used for the chronic analysis. HHA uses the 95th percentile of the exposure levels for each population subgroup as the default upper bound of exposures (DPR, 2009). The maximum detected level of imidacloprid in well-water (5.97 ppb) was used for the acute and chronic analyses because each detect reported in the memo was from a discrete well and averaging would not have been appropriate in this case.

The NOEL of 5.5 mg/kg/day based on effects in the DNT study in rats was used to calculate the acute or chronic risk in terms of margins of exposure (MOE; ratio of the NOEL over an estimate of human exposure). This NOEL was considered to be protective against acute and repeated exposures to any enhanced sensitivities intrinsic to pregnancy and fetal development. For both analyses, the target MOE was 100, assuming that humans are 10 times more sensitive than rats and that there is a 10-fold variation in the sensitivity of humans. A calculated MOE lower than the target (100) indicates a potential health concern.

Acute MOEs at the 95th percentile exposure were greater than 4,700 (4,735 to 20,247) for the US population and all population subgroups including those for nursing and non-nursing infants and children 1 through 12 years of age. The lowest acute MOE was for the subpopulation on non-nursing infants.

Chronic MOEs were greater than 9,000 (9,254 to 69,394) for the total US population and all population subgroups including those for nursing and non-nursing infants and children 1 through 12 years of age. The lowest chronic MOE was for the subpopulation on non-nursing infants.

Calculation of DPR Screening levels for Imidacloprid

We calculated a reference level for imidacloprid to be used by Environmental Monitoring Branch as a guide when requesting future human health evaluations for imidacloprid residues detected in ground water. Residues exceeding the reference level may pose a health concern and should be sent to HHA for further evaluation.

The reference is the residue level that will result in a 95th percentile MOE at the target MOE (100) for non-nursing infants (the population with highest consumption of drinking water) when using the NOEL of 5.5 mg/kg/day, the DEEM consumption data in a deterministic drinking water exposure analysis.

The reference levels for imidacloprid in drinking water based on acute and chronic exposures are summarized below (Table 1). While both reference levels are based on the subpopulation with the highest estimated risk (non-nursing infants), the acute reference level (283 ppb) was selected for use in screening for human health concerns because it was the lowest and therefore protective of acute and chronic exposures. For comparison, the DPR acute and chronic reference levels are both lower than either US EPA HHBP (Table 1).

Table 1. Acute and chronic reference levels for imidacloprid in drinking water

Acute or Chronic	Residue Level (ppb)	Subpopulation with Highest Water Intake per Bodyweight	Exposure Estimate	Calculated MOE	Target MOE ^c	Screening Level: Residue Level at Target (ppb) ^a	US EPA HHBPd (ppb)
Acute	5.97	Non-Nursing Infants	95 th Percentile	4,735 ^b	100	283	Acute, Children: 930
Chronic	5.97	Non-Nursing Infants	Average	9,254 ^b	100	552	General Population: 360

- a) Reference Level is the Residue Level that will result in a MOE at the Target MOE (ppb) = (DEEM MOE/Target MOE) x (Residue Level at DEEM MOE (ppb)).
- b) MOE (Margin of Exposure) for non-nursing infants.
- c) A target MOE of 100 is generally considered protective against the imidacloprid toxicity. This target takes into account uncertainty factors of 1 for interspecies sensitivity, 10 for intraspecies variability.
- d) HHBP: human health benchmark for pesticides.

Conclusions

1. The detected imidacloprid residue levels in CA well water ranging from 0.054 to 5.97 ppb should not be considered an acute or chronic health concern to residents that use the wells for drinking water.
2. We recommend that imidacloprid detections in CA wells be compared to a reference level of 283 ppb. Detected residues higher than this level may pose a health concern and should be sent to HHA for further evaluation.

References

- DPR. 2006. Imidacloprid Risk Characterization Document, Dietary and Drinking Water Exposure. <http://www.cdpr.ca.gov/docs/risk/rcd/imidacloprid.pdf>.
- DPR. 2009. MT-3 Version IV; Guidance for Dietary Exposure Assessment. <http://www.cdpr.ca.gov/docs/risk/riskpractice.htm>.
- NIH. 2018. PubChem Open Chemistry Database, Imidacloprid, Compound Summary for CID 86418. <https://pubchem.ncbi.nlm.nih.gov/compound/86418#section=Top>.
- USEPA. 2010. Imidacloprid: Revised Human-Health Risk Assessment for Proposed Section 3 Seed Treatment Uses on Bulb Vegetables (Crop Group 3); Cereal Grains (Crop Group 15); Root and Tuber Vegetables, Except Sugar Beet (Crop Subgroup IB); Tuberos and Corm Vegetables (Crop Subgroup I C); Leafy Vegetables, Except Brassica (Crop Subgroup 4A); Brassica Vegetables (Crop Group 5); Fruiting Vegetables (Crop Group 8); Cucurbit Vegetables (Crop Group 9), and Residential Crack and Crevice and Bed-Bug Uses. https://www3.epa.gov/pesticides/chem_search/hhbp/R181434.pdf.
- USEPA. 2011. Integrated Risk Information System (IRIS) Glossary https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do;jsessionid=VlwqcwYyLhUo1oDvgiO0TvQRBc0DnFfnaT0N8nvQPdtRKQaPCtCF!1236830639?details=&vocabName=IRIS%20Glossary&filterTerm=reference%20dose&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=reference%20dose&filterMatchCriteria=Contains.
- USEPA. 2017a. Fact Sheet: Human Health Benchmarks for Pesticides 2017 Update. <https://www.epa.gov/dwstandardsregulations/human-health-benchmarks-pesticides-drinking-water>.

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USEPA. 2017c. Human Health Benchmarks for Pesticides; Imidacloprid.
<https://ofmpub.epa.gov/apex/pesticides/f?p=109:3>.

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Appendices

Appendix 1. DPR Imidacloprid Memo 11 Jan 18 (2 pages)



Department of Pesticide Regulation



Brian R. Leahy
Director

MEMORANDUM

Edmund G. Brown Jr.
Governor

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

FROM: Pam Wofford
Environmental Program Manager II
Environmental Monitoring Branch
916-324-4297

DATE: January 11, 2018

SUBJECT: POTENTIAL HEALTH EFFECTS OF IMIDACLOPRID IN WELL WATER

Environmental Monitoring Branch monitored groundwater for imidacloprid and its major degradation products in 137 wells. From 2014 – 2017, imidacloprid was detected in 14 wells, with concentrations ranging from 0.054 – 5.97 ppb (Attachment 1). These concentrations are above our reporting limit of 0.05 ppb. Imidacloprid degradates were not detected in any well.

We request the Human Health Assessment Branch to determine whether these detections pose a significant risk to human health.

If you have any questions, please feel free to contact me.

Attachments

cc: Sheryl Gill



Attachment 1

Table 1. Results of Well Sampling for Imidacloprid

Well Location	Imidacloprid Concentration (ppb)
10M15S22E03	5.97*
10M14S22E31	0.665
10M15S24E14	0.644
10M14S23E35	0.238
2718S05E35	0.211
2716S06E07	0.194
54M16S24E12	0.124
10M14S23E34	0.12
54M17S25E11	0.074
10M15S21E09	0.072
10M15S22E06	0.072
10M14S22E14	0.066
10M14S23E33	0.065
10M14S22E02	0.054

* = Well services a house which is not being lived in

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Appendix 2. Acute Drinking Water Exposure Analysis (2 pages)

DEEM-FCID ACUTE Analysis for IMIDACLOPRID
 Residue file: IMD 09 Apr 18.R10
 Analysis Date: 04-09-2018/10:17:16
 NOEL (Acute) = 5.500000 mg/kg body-wt/day
 RAC/FF intake summed over 24 hours
 Run Comment: ""

Ver. 4.02, 05-10-c
 NHANES 2005-2010 2-Day
 Adjustment factor #2 NOT used.

Summary calculations--users:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	MOE	Exposure	MOE	Exposure	MOE
Total US Population:	0.000323	17025	0.000572	9620	0.001089	5050
Hispanic:	0.000340	16196	0.000698	7876	0.001218	4517
Non-Hisp-White:	0.000321	17119	0.000542	10143	0.001010	5447
Non-Hisp-Black:	0.000273	20149	0.000599	9179	0.001348	4080
Non-Hisp-Other:	0.000375	14679	0.000615	8942	0.001044	5265
Nursing Infants:	0.000717	7673	0.001257	4375	0.002160	2546
Non-Nursing Infants:	0.001162	4735	0.001533	3588	0.002031	2708
All Infants:	0.001125	4889	0.001511	3639	0.002036	2701
Female 13-50:	0.000317	17355	0.000462	11906	0.000686	8015
Children 1-2:	0.000466	11804	0.000695	7912	0.001798	3058
Children 3-5:	0.000371	14826	0.000575	9559	0.000995	5529
Children 6-12:	0.000291	18886	0.000474	11609	0.000782	7033
Adults 50-99:	0.000272	20247	0.000430	12793	0.000677	8129

DEEM-FCID Acute analysis for IMIDACLOPRID

Residue file name: H:\plohstroh\Documents\Memos\IMD and PNX in well water Jan 2018\Imidacloprid\DEEM Files\IMD 09 Apr 18.R10

Analysis Date 04-09-2018

Residue file dated: 04-09-2018/10:05:05

Reference dose (NOEL) = 5.5 mg/kg bw/day

EPA Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	Adj.Factors #2	Comment
8601000000	86A	Water, direct, all sources	0.005970	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.005970	1.000	1.000	

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Appendix 3. Chronic Drinking Water Exposure Analysis (2 pages)

 Total exposure by population subgroup

Population Subgroup	Total Exposure		
	mg/kg body wt/day	Percent of NOEL	Margin of Exposure
Total US Population	0.000121	0.00%	45,598
Hispanic	0.000118	0.00%	46,734
Non-Hisp-White	0.000124	0.00%	44,451
Non-Hisp-Black	0.000097	0.00%	56,739
Non-Hisp-Other	0.000142	0.00%	38,786
Nursing Infants	0.000137	0.00%	40,084
Non-Nursing Infants	0.000594	0.01%	9,254
Female 13+ PREG	0.000126	0.00%	43,748
Children 1-6	0.000145	0.00%	38,018
Children 7-12	0.000096	0.00%	57,500
Male 13-19	0.000079	0.00%	69,394
Female 13-19/NP	0.000090	0.00%	60,796
Male 20+	0.000112	0.00%	49,091
Female 20+/NP	0.000124	0.00%	44,338
Seniors 55+	0.000113	0.00%	48,738
All Infants	0.000451	0.01%	12,207
Female 13-50	0.000118	0.00%	46,450
Children 1-2	0.000166	0.00%	33,155
Children 3-5	0.000135	0.00%	40,747
Children 6-12	0.000100	0.00%	54,801
Youth 13-19	0.000085	0.00%	64,681
Adults 20-49	0.000120	0.00%	45,895
Adults 50-99	0.000117	0.00%	47,192
Female 13-49	0.000118	0.00%	46,686

DEEM-FCID Chronic analysis for IMIDACLOPRID

Residue file: H:\plohstroh\Documents\Memos\IMD and PNX in well water Jan 2018\Imidacloprid\DEEM Files\IMD 09 Apr 18.R10

Adjust. #2 NOT used

Analysis Date 04-09-2018

Residue file dated: 04-09-2018/10:05:05

Reference dose (NOEL) = 5.5 mg/kg bw/day

Food EPA Code	Crop Grp	Food Name	Residue (ppm)	Adj. Factors #1	#2
8601000000	86A	Water, direct, all sources	0.005970	1.000	1.000
8602000000	86B	Water, indirect, all sources	0.005970	1.000	1.000