Department of Pesticide Regulation

Brian R. Leahy
Director

Edmund G. Brown Jr.
Governor

M E M O R A N D U M

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 CONTAMINATED WITH PENOXSULAM

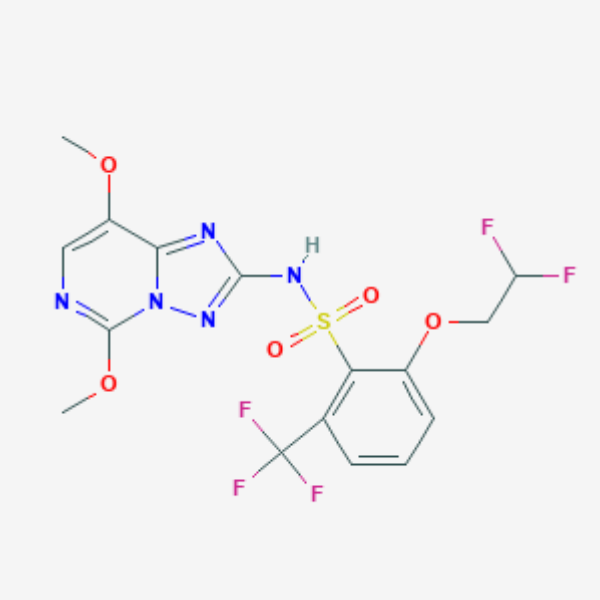
On January 11, 2018, the Human Health Assessment (HHA) Branch was notified by the Environmental Monitoring Branch that penoxsulam (PNX) was detected in the groundwater of 42 of 164 monitored wells in California. The detected levels of PNX ranged from the analytical reporting limit (RL = 0.05 ppb) to 0.338 parts-per-billion (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 penoxsulam 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 penoxsulam concentrations of 0.338 ppb in California well water do not pose acute or chronic health concerns.
3. Based on our assessment, we recommend that penoxsulam detections in California wells be compared to a reference level of 502 ppb. Detected resides higher than this level may pose a health concern and should be sent to HHA for further evaluation.

Background
Technical Name: penoxsulam
Chemical name: 2-(2,2-difluoroethoxy)-N-(5,8-dimethoxy-[1,2,4]triazolo[1,5-c]pyrimidin-2-yl)-6-(trifluoromethyl)benzenesulfonamide; Chemical Abstracts Service Registry Number (CAS) 219714-96-2 (NIH, 2018)

Chemical Structure:



Reference: (NIH, 2018)

Background
Penoxsulam is an herbicide from the class of sulfonamides that acts by inhibiting acetolactate synthase (ALS) in weeds, aquatic plants, and grasses (USEPA, 2004; USEPA, 2009). Penoxsulam is considered to have “minimal” acute toxicity in all categories (Category IV) (USEPA, 2009). The most sensitive target of toxicity observed in oral studies using rats and dogs following repeated exposures was the urothelium, which is the transitional epithelium that lines the urinary tract, the kidneys (renal pelvis), ureters, the urinary bladder, and the urethra (USEPA, 2009). Penoxsulam is classified as having suggestive evidence of carcinogenicity by the US EPA based on the incidence of mononuclear cell leukemia (MNCL) in a carcinogenicity study using rats (USEPA, 2009; USEPA, 2018). Per US EPA, “Penoxsulam is expected to be very mobile, but not very persistent, in either aqueous or terrestrial environments” (USEPA, 2004, pg. 2).

Summary of Toxicology

The toxicology database for PNX is limited. DPR has prepared a Summary of Toxicology Data for PNX (DPR, 2005), but has not previously conducted any human health risk evaluations for PNX. For the evaluation described in this memo, we used the DPR Summary of Toxicology Data to establish acute and chronic no-observed-effects-levels (NOELs). The acute NOEL of 25 mg/kg/day was based on effects in a developmental toxicity study in rabbits. Maternal effects from this study included decreased activity, death, spontaneous abortion, and changes to fecal parameters and developmental effects included fetal resorptions. The chronic NOEL of 5 mg/kg/day was based on effects in two chronic toxicity studies in rats. Effects included perineal soiling and changes to hematologic and urinalysis parameters.

In 2017, US EPA Office of Ground Water and Drinking Water established a chronic, non-cancer human health benchmark for pesticides (HHBP) for PNX (941 ppb) that was based on a population adjusted dose (cPAD) of 0.147 mg/kg/day based on a no-observed-adverse-effects-level (NOAEL) of 14.7 mg/kg/day from a chronic toxicity study using beagle dogs and a total uncertainty factor (UF) of 100 (USEPA, 2009; USEPA, 2017b). A cPAD or a chronic reference dose (cRfD) is defined as "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime" (USEPA, 2011). An acute RfD was not established (USEPA, 2009). Per US EPA, "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" (USEPA, 2017a), pg. 1).

Evaluation of the Penoxsulam Residue

Deterministic Exposure Analysis

We estimated the acute and chronic exposures to penoxsulam 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 penoxsulam in well-water (0.338 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.

An acute NOEL for penoxsulam (25 mg/kg/day) based on effects in a developmental toxicity study using rabbits and a chronic NOEL (5 mg/kg/day) based on effects in two chronic toxicity studies in rats were 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). 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 were greater than 380,000 (380,150 to > 1,000,000) 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 acute MOE was for the subpopulation on non-nursing infants.

Chronic MOEs were greater than 148,000 (148,585 to > 1,000,000) 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 Reference levels for Penoxsulam

We calculated a reference level for penoxsulam to be used by Environmental Monitoring Branch as a guide when requesting future human health evaluations for penoxsulam 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 an MOE at the target (100) for non-nursing infants (the population with highest consumption of drinking water) when using the chronic NOEL of 5 mg/kg/day and the DEEM consumption data in a deterministic drinking water exposure analysis.

The reference levels for penoxsulam 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 chronic reference level (502 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 the US EPA chronic HHBP (Table 1).

Table 1. Acute and chronic reference levels for penoxsulam 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	0.338	Non-Nursing Infants	95th Percentile	380,150[b]	100	1285	NA
Chronic	0.338	Non-Nursing Infants	Average	148,585[b]	100	502	General Population: 941

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 penoxsulam toxicity. This target takes into account uncertainty factors of 10 for interspecies sensitivity, 10 for intraspecies variability.
d) HHBP: human health benchmark for pesticides.

Conclusions

1. The detected penoxsulam residue levels in CA well water ranging from 0.050 to 0.338 ppb should not be considered an acute or chronic health concern to residents that use the wells for drinking water.
2. We recommend that penoxsulam detections in CA wells be compared to a reference level of 502 ppb. Detected resides higher than this level may pose a health concern and should be sent to HHA for further evaluation.

References

DPR. 2005. Summary of Toxicology Data; Penoxsulam. http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/5889.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, Penoxsulam, Compound Summary for CID 11784975. https://pubchem.ncbi.nlm.nih.gov/compound/11784975#section=Top.

USEPA. 2004. Pesticide Fact Sheet; Penoxsulam. https://www3.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-119031_27-Sep-04.pdf.

USEPA. 2009. Penoxsulam: Revised Human Health Risk Assessment for Proposed Uses on Grapes and Tree Nuts. https://www.regulations.gov/document?D=EPA-HQ-OPP-2008-0526-0007.

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.

USEPA. 2017b. Human Health Benchmarks for Pesticides; Penoxsulam. https://ofmpub.epa.gov/apex/pesticides/f?p=109:3.

USEPA. 2018. Evaluating Pesticides for Carcinogenic Potential. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/evaluating-pesticides-carcinogenic-potential#b.

Appendices

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

Brian R. Leahy
Director

Department of Pesticide Regulation

Edmund G. Brown Jr.
Governor

MEMORANDUM

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

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

DATE: January 11, 2018

SUBJECT: POTENTIAL HEALTH EFFECTS OF PENOXSULAM IN WELL WATER

As part of an ongoing study on rice pesticides, the Environmental Monitoring Branch monitored groundwater for penoxsulam in 164 wells. From 2013 to 2015, penoxsulam was detected in 42 wells; 11 of these wells had concentrations at or above the analytical method reporting limit of 0.05 ppb. The maximum concentration of penoxsulam detected was 0.338 ppb (Attachment 1).

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.

Attachment

cc: Sheryl Gill

Attachment 1

Table 1. Results of Well Sampling for Penoxsulam

Well Location	Site	Penoxsulam Detected (ppb)
16N/03E-31	51-04	**0.338**
12N/04E-03	51-17	**0.257**
12N/04E-35	51-21	**0.132**
15N/02E-35	51-26	**0.125**
15N/02E-14	51-09	**0.092**
13N/04E-34	51-70	**0.080**
12N/04E-34	51-36	**0.071**
16N/04E-27	58-23	**0.070**
19N/02E-02	04-08	**0.057**
12N/04E-04	51-63	**0.057**
12N/04E-02	51-67	**0.050**[a]
16N/02E-25	51-48	*0.042*
16N/03E-31	51-05	*0.036*
20N/02E-34	04-10	*0.029*
15N/03W-07	06-01	*0.028*
19N/03W-10	11-23	*0.024*
20N/02W-02	11-14	*0.022*
15N/02E-11	51-06	*0.022*
16N/03E-31	51-50	*0.022*
12N/04E-02	51-61	*0.021*
19N/02W-05	11-06	*0.020*
16N/03E-30	51-46	*0.019*
20N/02W-12	11-13	*0.016*
13N/05E-32	51-16	*0.016*
15N/02E-01	51-69	*0.016*
18N/03W-19	11-20	*0.015*
16N/03E-19	51-03	*0.014*
15N/02E-36	51-25	*0.013*
12N/04E-04	51-45	*0.011*
15N/02E-14	51-51	*0.011*
14N/02E-13	51-28	*0.010*
15N/02E-22	51-11	*0.009*
20N/01W-30	11-30	*0.008*
17N/02E-08	04-22	*0.007*
18N/01E-35	04-25	*0.006*
19N/02E-25	04-51	*0.006*
16N/04E-28	58-05	*0.006*
19N/02W-06	11-24	*0.005*
20N/02W-19	11-27	*0.005*
20N/02E-08	04-06	*0.004*
20N/02W-20	11-28	*0.004*
13N/04E-22	51-14	*0.004*

a. Concentrations below the line are less than the 0.05 ppb reporting limit and are considered trace detections.

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

Ver. 4.02, 05-10-c
DEEM-FCID ACUTE Analysis for PENOXSULAM NHANES 2005-2010 2-Day
Residue file: PNX Acute 20 Feb 18.R10 Adjustment factor #2 NOT used.
Analysis Date: 02-20-2018/10:01:51 Residue file dated: 02-20-2018/09:48:47
NOEL (Acute) = 25.000000 mg/kg body-wt/day
RAC/FF intake summed over 24 hours
Run Comment: ""

Summary calculations--users:

	95th Percentile Exposure	95th Percentile MOE	99th Percentile Exposure	99th Percentile MOE	99.9th Percentile Exposure	99.9th Percentile MOE
Total US Population:	0.000018	>1000000	0.000032	772374	0.000062	405444
Hispanic:	0.000019	>1000000	0.000040	632366	0.000069	362670
Non-Hisp-White:	0.000018	>1000000	0.000031	814405	0.000057	437323
Non-Hisp-Black:	0.000015	>1000000	0.000034	736949	0.000076	327617
Non-Hisp-Other:	0.000021	>1000000	0.000035	717918	0.000059	422773
Nursing Infants:	0.000041	616072	0.000071	351317	0.000122	204416
Non-Nursing Infants:	0.000066	380150	0.000087	288087	0.000115	217437
All Infants:	0.000064	392544	0.000086	292206	0.000115	216872
Female 13-50:	0.000018	>1000000	0.000026	955903	0.000039	643505
Children 1-2:	0.000026	947730	0.000039	635292	0.000102	245547
Children 3-5:	0.000021	>1000000	0.000033	767457	0.000056	443958
Children 6-12:	0.000016	>1000000	0.000027	932087	0.000044	564685
Adults 50-99:	0.000015	>1000000	0.000024	>1000000	0.000038	652644

DEEM-FCID Acute analysis for PENOXSULAM
Residue file name: H:\plohstroh\Documents\Memos\IMDCPD and PNXLM in well water Jan 2018\Penoxsulam\DEEM Files\PNX Acute 20 Feb
Analysis Date 02-20-2018 Residue file dated: 02-20-2018/09:48:47
Reference dose (NOEL) = 25 mg/kg bw/day

EPA Code	Crop Grp	Food Name	Def Res (ppm)	Adj.Factors #1	#2	Comment
8601000000	86A	Water, direct, all sources	0.000338	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.000338	1.000	1.000	

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

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for PENOXSULAM NHANES 2005-2010 2-day
Residue file name: H:\plohstroh\Documents\Memos\IMD and PNX in well water Jan 2018\Penoxsulam\DEEM Files\PNX Chronic 28 Mar 18.
Adjustment factor #2 used.
Analysis Date 03-28-2018/12:22:55 Residue file dated: 03-28-2018/12:21:19
NOEL (Chronic) = 5 mg/kg bw/day

Total exposure by population subgroup

Population Subgroup	Total Exposure mg/kg body wt/day	Percent of NOEL	Margin of Exposure
Total US Population	0.000007	0.00%	732,166
Hispanic	0.000007	0.00%	750,412
Non-Hisp-White	0.000007	0.00%	713,749
Non-Hisp-Black	0.000005	0.00%	911,062
Non-Hisp-Other	0.000008	0.00%	622,786
Nursing Infants	0.000008	0.00%	643,628
Non-Nursing Infants	0.000034	0.00%	148,585
Female 13+ PREG	0.000007	0.00%	702,460
Children 1-6	0.000008	0.00%	610,461
Children 7-12	0.000005	0.00%	923,284
Male 13-19	0.000004	0.00%	>1,000,000)
Female 13-19/NP	0.000005	0.00%	976,198
Male 20+	0.000006	0.00%	788,258
Female 20+/NP	0.000007	0.00%	711,930
Seniors 55+	0.000006	0.00%	782,581
All Infants	0.000026	0.00%	196,005
Female 13-50	0.000007	0.00%	745,844
Children 1-2	0.000009	0.00%	532,378
Children 3-5	0.000008	0.00%	654,273
Children 6-12	0.000006	0.00%	879,936
Youth 13-19	0.000005	0.00%	>1,000,000)
Adults 20-49	0.000007	0.00%	736,944
Adults 50-99	0.000007	0.00%	757,757
Female 13-49	0.000007	0.00%	749,637

Evaluation Copy Ver. 4.02, 05-10-c
DEEM-FCID Chronic analysis for PENOXSULAM
Residue file: H:\plohstroh\Documents\Memos\IMD and PNX in well water Jan 2018\Penoxsulam\DEEM Files\PNX Chronic 28 Mar 18.R10
Adjust. #2 used
Analysis Date 03-28-2018 Residue file dated: 03-28-2018/12:21:19
Reference dose (NOEL) = 5 mg/kg bw/day

Food EPA Code	Crop Grp	Food Name	Residue (ppm)	Adj.Factors #1	#2
8601000000	86A	Water, direct, all sources	0.000338	1.000	1.000
8602000000	86B	Water, indirect, all sources	0.000338	1.000	1.000