



TO: Pam Wofford, Chief
Environmental Monitoring Branch

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

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

DATE: June 6, 2019

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

On May 10, 2019, the Department of Pesticide Regulation (DPR), Human Health Assessment (HHA) Branch was notified by the Environmental Monitoring (EMON) Branch that fludioxonil was detected in the water of one (1) well. The detected levels of ranged from 0.066 to 0.165 parts-per-billion (ppb) with an analytical reporting limit (RL) of 0.05 ppb. EMON requested that HHA determine whether or not the reported residue levels posed a health concern for individuals using the well as a source of drinking water. This memo is in response to that request.

Conclusions and Recommendations:

1. HHA evaluated the acute and chronic human health risks of the maximum level of fludioxonil measured in well water using toxicological endpoints established by United States Environmental Protection Agency (US EPA) 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 fludioxonil concentrations of 0.066-0.165 ppb in California well water do not pose acute or chronic health concerns.
3. Based on our assessment, we recommend that fludioxonil detections in California wells be compared to a reference level of 331 ppb. Detected residues higher than this level may pose a health concern and should be sent to HHA for further evaluation.

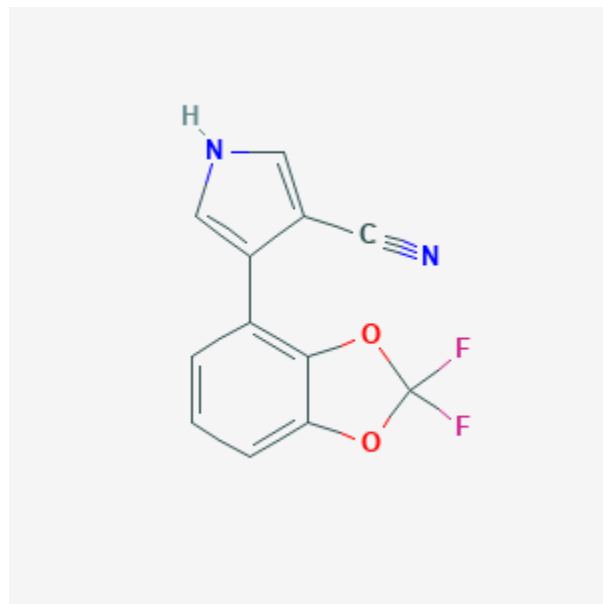
Background

Technical Name: Fludioxonil

Chemical name: 4-(2,2-difluoro-1,3-benzodioxol-4-yl)-1H-pyrrole-3-carbonitrile;
Chemical Abstracts Service Registry Number (CAS) 131341-86-1

<https://pubchem.ncbi.nlm.nih.gov/compound/86398#section=Molecular-FormulaChemical>

Structure:



Reference: <https://pubchem.ncbi.nlm.nih.gov/compound/86398#section=Molecular-Formula>

Fludioxonil is a non-systemic fungicide. Per US EPA (pg. 3) (USEPA, 2011b): “Fludioxonil is a phenylpyrrole derivative of an antibiotic produced by the soil-borne bacterium *Pseudomonas*. It is intended to control certain post-harvest diseases caused by *Monilinia fructicola* and *M. laxa* (brown rot), *Botrytis cinerea* (gray mold), and *Rhizopus stolonifer* (Rhizopus rot). A suggested mode of action of phenylpyrroles derivatives is inhibition of the trans-membrane transport associated with glucose phosphorylation.” In the US, fludioxonil is registered “for use on a variety of field and vegetable crops, fruit trees, berries, herbs, and grasses. It can be applied as a seed treatment, an at-planting soil application, and/or broadcast foliar application” (pg. 4) (USEPA, 2012).

Fludioxonil is considered by US EPA to be of low acute toxicity (Toxicity categories III and IV based on the oral and dermal LD50 level and inhalation LC50 level in rodents) and it does not act as a dermal sensitizer (USEPA, 2012). Signs of subchronic and chronic toxicity in rats and mice include decrements in body weight and food consumption and pathological changes to the liver and kidneys, and in dogs included diarrhea and pathological changes to the liver (USEPA, 2012). Developmental toxicity was not observed in rabbits while an increased litter-incidence of dilated renal pelvis was observed in rats concurrent with maternal toxicity in the highest dose

tested (1000 mg/kg/day) (USEPA, 2012). Tests for mutagenicity were largely negative except for the induction of polyploidy in an *in vitro* cytogenic assay and the induction of micronuclei *in vivo*. The results for three follow-up aneuploidy studies were negative (USEPA, 2012). Liver tumors (hepatocellular adenomas and carcinomas) were observed in female rats and no tumors were observed in mice (USEPA, 2012). While there was statistical significance in trend and pairwise tests for combined adenomas and carcinomas, the incidence was within the range observed for historical controls. USEPA classified fludioxonil as a Group D chemical (“not classifiable as to human carcinogenic potential”) and based on the above data, further concluded that fludioxonil posed a “negligible cancer risk” (USEPA, 2012).

US EPA considers fludioxonil to be stable, “slightly to moderately” mobile in aqueous environments, and to be a “primary concern” for surface water (USEPA, 2011b). On the other hand, US EPA considers fludioxonil to have “moderately high” adsorption coefficients and “low” solubility and to be “moderately persistent to persistent in surface soils” (USEPA, 2011b). In California, fludioxonil is on the DPR Groundwater Protection List of pesticides with the potential to pollute ground water (DPR, 2019)¹.

Summary of Toxicology

HHA has not conducted risk assessment for fludioxonil and has not established critical Points of Departure (PoDs) and Reference Doses (RfDs). However, the HHA Data Review Section reviewed the registrant submitted studies for registration with DPR and prepared a summary of toxicology data in 1997. In addition, the HHA Toxicology and Dose Response and Risk Assessment sections (TDRAS and RAS) reviewed the available human health risk assessment prepared by other regulatory agencies (US EPA, European Food Safety Authority (EFSA), etc.). As a result, HHA adopted the 2012 US EPA acute PoDs and RfDs to use for evaluating fludioxonil residues in fresh produce for the DPR California Pesticide Residue Monitoring Program (CPRMP) and to establish health-based screening levels for fludioxonil residue in manufactured cannabis products for the California Bureau of Cannabis Control.

For this memo, HHA also used the 2012 US EPA PoDs to evaluate the acute and chronic dietary risk posed by fludioxonil in drinking water. The acute PoD was a no-observed-adverse-effects-level (NOAEL) of 100 mg/kg/day based on an increased incidence of dilated renal pelvis in

¹ “The Department of Pesticide Regulation’s (DPR’s) Ground Water Protection Program is mandated by the Pesticide Contamination Prevention Act (PCPA) (Statutes of 1985, Chapter 1298, Section 1). The PCPA was enacted in 1985 to prevent further pesticide pollution of California ground water that may be used for drinking water. The PCPA outlines procedures for (1) gathering physical and chemical data on pesticides, (2) establishing specific numerical values (SNVs [threshold values]) for specified types of those data that the PCPA associates with the potential of a pesticide to leach through soil to ground water, (3) identifying pesticides that “exceed” those SNVs, and (4) placing pesticides that “exceed” the SNVs and are applied in specified ways on the Groundwater Protection List (GWPL) (Title 3, California Code of Regulations [3 CCR] section 6800[b]). DPR is then required to monitor ground water for the GWPL pesticides to determine if these pesticides have migrated to ground water as a result of legal agricultural use” (pg. 1) (DPR. 2013).

fetuses and litters observed in a rat developmental toxicity study (USEPA, 2012). This PoD was used to evaluate the acute risk from of fludioxonil residues in well water to infants, children and women of reproductive age (13-49 years old). The chronic PoD was a NOAEL of 3.3 mg/kg/day based on decrements in body weight gain observed in a one-year feeding study in dogs (USEPA, 2012). This PoD was used to evaluate the chronic risk of fludioxonil in drinking water.

Evaluation of the Fludioxonil Residue in Well Water

Drinking Water Exposure Analysis

HHA estimated the acute and chronic exposures to fludioxonil 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 for acute exposures (DPR, 2009). The maximum detected level of fludioxonil in well-water (0.165 ppb) was used for the acute and chronic analyses.

The acute PoD of 100 mg/kg/day based on effects in the developmental study in rats was used to calculate the acute risk was in terms of margins of exposure (MOE; the PoD divided by the estimated drinking water exposure). This PoD was used to evaluate the risk posed by acute exposures to infant, fetal, and pregnant subpopulations who might have higher susceptibilities to any adverse effects. The chronic PoD of 3.3 mg/kg/day based on effects in the one-year dietary study in dogs was used to evaluate chronic risk in the same manner. The target MOE for both analyses was 100, assuming that humans are 10 times more sensitive than rats or dogs and that there is a 10-fold variation in the sensitivity of humans. A calculated MOE lower than the target (100) would indicate a potential health concern.

Acute MOEs at the 95th percentile exposure were greater than the maximum (>1,000,000) for the US population and all population subgroups including those for nursing and non-nursing infants and children 1 through 12 years of age.

Chronic MOEs were greater than 200,000 (200,887 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 of non-nursing infants.

Calculation of DPR Screening levels for Fludioxonil

HHA calculated a reference level for fludioxonil to be used by the EM Branch as a guide when requesting future human health evaluations for fludioxonil 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 level is the estimated residue level that would result in a 2-day average MOE at the target (100) for non-nursing infants (the population with highest consumption of drinking water) when using the chronic PoD of 3.3 mg/kg/day and the DEEM consumption data in a deterministic drinking water exposure analysis. This reference level will be protective of both acute and chronic exposures. The results of our analyses and the reference level for fludioxonil in drinking water are summarized below (Table 1).

For this type of evaluation, it is HHA's standard practice to compare relevant human-health reference levels used by other regulatory agencies with the results of our own evaluations whenever possible. In 2017, US EPA Office of Ground Water and Drinking Water established acute and chronic human health benchmarks for pesticides (HHBPs) for fludioxonil (USEPA, 2017c). 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."

The acute HHBP (30,000 ppb) for women of reproductive age (13-49 years old) was calculated using an acute population adjusted dose (aPAD) of 1 mg/kg/day. The aPAD was based on the above acute PoD of 100 mg/kg/day from a developmental study using rats and a total uncertainty factor (UF) of 100 (USEPA, 2017b; USEPA, 2017a; 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, 2011a).

The chronic HHBP (200 ppb) for the US general population was calculated using a chronic population adjusted dose (cPAD) of 0.03 mg/kg/day. The cPAD was based on the chronic PoD of 3.3 mg/kg/day from a one-year feeding study using dogs and a total uncertainty factor (UF) of 100 (USEPA, 2017b; USEPA, 2017a; USEPA, 2017c). The cPAD is considered to be the maximum, safe, chronic or lifetime exposure level (USEPA, 2011a).

The US EPA HHBP levels are provided for comparison (Table 1). While the chronic HHBP is lower than the HHA reference level (200 vs. 331 ppb), both values are similar in magnitude. The HHA reference level was calculated using distribution of drinking water consumption, while the HHBP was calculated using a single consumption estimate.

Table 1. Acute and chronic reference levels for fludioxonil 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 HHBP ^d (ppb)
Acute	0.165	Non-Nursing Infants	95 th Percentile	>1,000,000 ^b	100	331 ^e	30,000 ^f
Chronic	0.165	Non-Nursing Infants	Average	200,887 ^b	100	331	200 ^g

- 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) The target MOE of 100 takes into account uncertainty factors of 10 for interspecies sensitivity, 10 for intraspecies variability.
- d) HHBP: human health benchmark for pesticides: fludioxonil (USEPA, 2017c).
- e) Calculated using chronic PoD and exposure.
- f) HHBP is for Acute, Females 13-49 years.
- g) HHBP is for General population.

Conclusions

1. The detected fludioxonil residue levels in California well water ranging from 0.066 to 0.165 ppb should not be considered an acute or chronic health concern to residents that use the well for drinking water.
2. We recommend that fludioxonil detections in California wells be compared to a reference level of 331 ppb. Detected residues higher than this level may pose a health concern and should be sent to HHA for further evaluation.

References

- DPR. 2009. MT-3 Version IV; Guidance for Dietary Exposure Assessment.
- DPR. 2013. Memorandum to D. Duncan, Branch Chief. Guidelines for identifying pesticides to be added to and removed from the Groundwater Protection List: Title 3, California Code of Regulations Section 6800(B).
- DPR. 2019. California Code of Regulations (Title 3. Food and Agriculture); Division 6. Pesticides and Pest Control Operations; Division 6. Pesticides and Pest Control Operations; Chapter 4. Environmental Protection; Subchapter 1. Groundwater; Article 1. Pesticide Contamination Prevention; 6800. Groundwater Protection List.
- USEPA. 2011a. Integrated Risk Information System (IRIS) Glossary
- USEPA. 2011b. Tier I Drinking Water Assessment in Support of Proposed or Amended Tolerances for the Fludioxonil IR-4 Uses on Ginseng; Onion Subgroups 3-07 A and B; Berry and Small Fruit Subgroups 13-07 A, B, F and G; Fruiting Vegetable Group 8-10, Except Tomato; Tomato; Leafy Vegetable Except Brassica Subgroup 4A; Pome Fruit Group 11-10; Citrus Group 10-10; Potato; Pineapple; Dragon Fruit; Avocado; Mango; Other Various Tropical Fruits.
- USEPA. 2012. Fludioxonil. Tolerance Petitions for Residues in/on Ginseng, Leafy Petioles Crop Subgroup 4B, Pineapple (post-harvest treatment), Tuberous and Corm Vegetable Subgroup 1C, Tropical Fruit (post-harvest treatment), Bulb Onion Subgroup 3-07A, Green Onion subgroup 3-07B, Caneberry Subgroup 13-07A, Bushberry Subgroup 13-07B, Small Fruit Vine Climbing Subgroup 13-07F (except fuzzy kiwifruit), Low-Growing Berry Subgroup 13-07G (except cranberry), Fruiting Vegetable Group 8-10 (except tomato), Citrus Fruit Group 10-10, Pome Fruit Group 11-10, Leafy Vegetable (except Brassica) Subgroup 4A, Dragon Fruit, and Tomato (post-harvest treatment). Human-Health Risk Assessment.
- USEPA. 2017a. Fact Sheet: Human Health Benchmarks for Pesticides 2017 Update.
- USEPA. 2017b. Human Health Benchmarks for Pesticides: Updated 2017 Technical Document.
- USEPA. 2017c. Human Health Benchmarks for Pesticides; Fludioxonil.

Appendices

Appendix 1. DPR Fludioxonil Emails 09 May 19 (1 pages)

From: Wofford, Pam@CDPR <Pam.Wofford@cdpr.ca.gov>
Sent: Thursday, May 09, 2019 3:24 PM
To: DuTeaux, Shelley@CDPR <Shelley.DuTeaux@cdpr.ca.gov>
Cc: Morrison, Karen@CDPR <Karen.Morrison@cdpr.ca.gov>; Cuevas, Jesse@CDPR <Jesse.Cuevas@cdpr.ca.gov>; Dias, Joy@CDPR <Joy.Dias@cdpr.ca.gov>
Subject: FW: Fludioxonil

Shelley,

We would appreciate a memo on the health concern for the following well/active ingredient detection. We have only found this pesticide at this one well but it is the second year in a row so we will assume it was not a “phantom” detection. All QA/QC indicates that the analysis was appropriate. We would like the memo so we can send a letter to the well owner. We appreciate your staff’s time and all of the previous memos they have provided us.

Thanks
Pam

From: Dias, Joy@CDPR <Joy.Dias@cdpr.ca.gov>
Sent: Thursday, May 09, 2019 2:57 PM
To: Wofford, Pam@CDPR <Pam.Wofford@cdpr.ca.gov>
Subject: Fludioxonil

The Groundwater Protection Program detected fludioxonil in the water of one well at levels ranging from 0.066 to 0.165 parts-per-billion (ppb) with an analytical reporting limit (RL) of 0.05 ppb. We would like to request that HHA determine whether or not there is a health concern for individuals using this well as a source of drinking water

Thanks,

Joy Dias
Senior Environmental Scientist, Supervisory
California Department of Pesticide Regulation
Environmental Monitoring Branch
Groundwater Protection Program
1001 I St
Sacramento, CA 95817
916-324-4183

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

DEEM-FCID ACUTE Analysis for FLUDIOXONIL
 Residue file: Fludioxonil Water 10 May 19.R10
 Analysis Date: 05-10-2019/11:29:29
 NOEL (Acute) = 100.000000 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.

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Summary calculations--users:

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure	MOE	Exposure	MOE	Exposure	MOE
Total US Population:	0.000009	>1000000	0.000016	>1000000	0.000030	>1000000
Hispanic:	0.000009	>1000000	0.000019	>1000000	0.000034	>1000000
Non-Hisp-White:	0.000009	>1000000	0.000015	>1000000	0.000028	>1000000
Non-Hisp-Black:	0.000008	>1000000	0.000017	>1000000	0.000037	>1000000
Non-Hisp-Other:	0.000010	>1000000	0.000017	>1000000	0.000029	>1000000
Nursing Infants:	0.000020	>1000000	0.000035	>1000000	0.000060	>1000000
Non-Nursing Infants:	0.000032	>1000000	0.000042	>1000000	0.000056	>1000000
Female 13+ PREG:	0.000008	>1000000	0.000011	>1000000	0.000015	>1000000
Children 1-6:	0.000011	>1000000	0.000017	>1000000	0.000030	>1000000
Children 7-12:	0.000008	>1000000	0.000013	>1000000	0.000020	>1000000
Male 13-19:	0.000007	>1000000	0.000011	>1000000	0.000026	>1000000
Female 13-19/NP:	0.000008	>1000000	0.000012	>1000000	0.000017	>1000000
Seniors 55+:	0.000007	>1000000	0.000011	>1000000	0.000017	>1000000
All Infants:	0.000031	>1000000	0.000042	>1000000	0.000056	>1000000
Children 1-2:	0.000013	>1000000	0.000019	>1000000	0.000050	>1000000
Children 3-5:	0.000010	>1000000	0.000016	>1000000	0.000027	>1000000
Children 6-12:	0.000008	>1000000	0.000013	>1000000	0.000022	>1000000
Youth 13-19:	0.000008	>1000000	0.000012	>1000000	0.000017	>1000000
Adults 20-49:	0.000009	>1000000	0.000013	>1000000	0.000018	>1000000
Adults 50-99:	0.000008	>1000000	0.000012	>1000000	0.000019	>1000000
Female 13-49:	0.000009	>1000000	0.000013	>1000000	0.000019	>1000000

DEEM-FCID Acute analysis for FLUDIOXONIL

Residue file name: H:\plohstroh\Documents\Memos\Fludioxonil 10 May 19\Fludioxonil Water 10 May 19.R10

Analysis Date 05-10-2019

Residue file dated: 05-10-2019/11:23:57

Reference dose (NOEL) = 100 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	0.000165	1.000	1.000	
8602000000	86B	Water, indirect, all sources	0.000165	1.000	1.000	

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

Evaluation Copy
 DEEM-FCID Chronic analysis for FLUDIOXONIL
 Residue file name: H:\plohstroh\Documents\Memos\Fludioxonil 10 May 19\Fludioxonil
 Water 10 May 19.R10

Ver. 4.02, 05-10-c
 NHANES 2005-2010 2-day

Adjustment factor #2 NOT used.
 Analysis Date 05-10-2019/11:35:35 Residue file dated: 05-10-2019/11:23:57
 NOEL (Chronic) = 3.3 mg/kg bw/day

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 Total exposure by population subgroup
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Population Subgroup	Total Exposure		
	mg/kg body wt/day	Percent of NOEL	Margin of Exposure
Total US Population	0.000003	0.00%	989,888
Hispanic	0.000003	0.00%	>1,000,000)
Non-Hisp-White	0.000003	0.00%	964,988
Non-Hisp-Black	0.000003	0.00%	>1,000,000)
Non-Hisp-Other	0.000004	0.00%	842,006
Nursing Infants	0.000004	0.00%	870,185
Non-Nursing Infants	0.000016	0.00%	200,887
Female 13+ PREG	0.000003	0.00%	949,726
Children 1-6	0.000004	0.00%	825,343
Children 7-12	0.000003	0.00%	>1,000,000)
Male 13-19	0.000002	0.00%	>1,000,000)
Female 13-19/NP	0.000003	0.00%	>1,000,000)
Male 20+	0.000003	0.00%	>1,000,000)
Female 20+/NP	0.000003	0.00%	962,529
Seniors 55+	0.000003	0.00%	>1,000,000)
All Infants	0.000012	0.00%	264,999
Female 13-50	0.000003	0.00%	>1,000,000)
Children 1-2	0.000005	0.00%	719,775
Children 3-5	0.000004	0.00%	884,577
Children 6-12	0.000003	0.00%	>1,000,000)
Youth 13-19	0.000002	0.00%	>1,000,000)
Adults 20-49	0.000003	0.00%	996,348
Adults 50-99	0.000003	0.00%	>1,000,000)
Female 13-49	0.000003	0.00%	>1,000,000)

Food EPA Code	Crop Grp	Food Name	Residue (ppm)	Adj. Factors #1	Adj. Factors #2
8601000000	86A	Water, direct, all sources	0.000165	1.000	1.000
8602000000	86B	Water, indirect, all sources	0.000165	1.000	1.000