M E M O R A N D U M

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DATE: February 28, 2023

SUBJECT: RISKS FROM HUMAN EXPOSURE TO NORFLURAZON AND ITS DEGRADATE DESMETHYLNORFLURAZON IN GROUNDWATER

On December 1, 2022, the Department of Pesticide Regulation's (DPR) Human Health Assessment Branch (HHA) was notified by the Environmental Monitoring Branch (EMB) that routine monitoring conducted by the Groundwater Protection Program (GWPP) detected norflurazon and its degradate, desmethylnorflurazon, in California's groundwater. The highest detected concentration of norflurazon in groundwater was 2.48 ppb (with 1.44 ppb of desmethylnorflurazon) and the highest detected concentration of desmethylnorflurazon in groundwater was 1.97 ppb (with 0.283 ppb of norflurazon). EMB requested that HHA determine if the highest detected concentration of each residue poses health concerns for individuals using the groundwater as a source of drinking water and provide a Human Health Reference Level (HHRL) for screening detections of norflurazon and desmethylnorflurazon in groundwater (see request, Appendix 1). This memorandum is in response to that request.

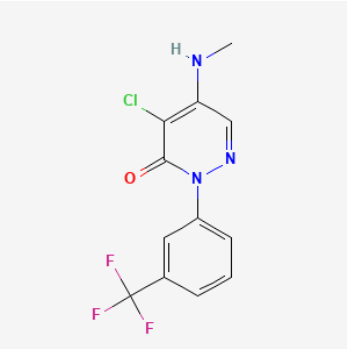
Conclusions and Recommendations:

1. HHA calculated Human Health Reference Levels (HHRLs) to be used when residues of norflurazon and its degradate, desmethylnorflurazon, are detected in groundwater or drinking 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. Residue levels of norflurazon and desmethylnorflurazon, alone or in combination, equal to or less than the DPR HHRL of 150 ppb in drinking water are not expected to pose a risk to human health, including for sensitive subpopulations. Thus, neither the highest detected individual nor the combined residual levels for norflurazon and desmethylnorflurazon in groundwater should be considered acute or chronic health concerns.

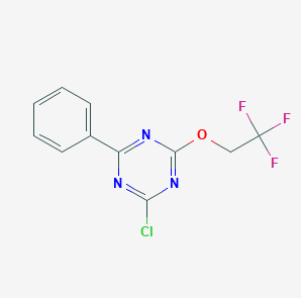
Background

Technical Name: Norflurazone
Chemical Name: 4-Chloro-5-(methylamino)-2-[3-(trifluoromethyl)phenyl]pyridazin-3-one
Chemical Abstracts Service Registry Number (CAS): 27314-13-2 (NIH, 2022a)
Chemical Structure:



(NIH, 2022a)

Technical Name: Desmethylnorflurazon
Chemical Name: 2-Chloro-4-phenyl-6-(2,2,2-trifluoroethoxy)-1,3,5-triazine
Chemical Abstracts Service Registry Number (CAS): 112748-69-3 (NIH, 2022b)
Chemical Structure:



(NIH, 2022b)

Norflurazon is a pyridazinone herbicide to control or suppress germinating grass and broadleaf weeds by disrupting carotenoid synthesis (US EPA, 2001; US EPA, 2017b). It is a broad spectrum herbicide registered for use on a variety of agricultural crops including alfalfa, cotton,

hops, nursery stock, nuts, peanuts, soybeans, and various fruits and vegetables, and on non-crop areas such as fence lines, equipment lots, ditchbanks, on-farm roads, turn rows, and other on-farm non-crop land areas (US EPA, 2017b). Norflurazon is not registered for residential uses (US EPA, 1996; US EPA, 2017b). Norflurazon products were first registered in 1974 by US EPA and then in 1988 in California. Currently there are three products with active registrations in California (DPR, 2022e). According to the latest data available from the DPR Pesticide Use Reporting (PUR) database, 12,658 pounds of norflurazon were used in 387 California agricultural applications in 2018 (DPR, 2018).

Desmethylnorflurazon is a major degradate in soil and a metabolite of norflurazon in animals resulting from N-demethylation (US EPA, 2001; US EPA, 2017b). The Metabolism Assessment Review Committee (MARC) of the Health Effects Division at US EPA concluded that desmethylnorflurazon (conjugated and free) is a residue of concern for human health (US EPA, 2017b). Residual desmethylnorflurazon was found in plant crops, livestock, and in drinking water (US EPA, 2017b; US EPA, 2017a; US EPA, 2022g). No studies were found that evaluated the toxicity for desmethylnorflurazon. Based on molecular weights of desmethylnorflurazon and norflurazon (289.64 and 303.67 respectively), 0.95 ppm desmethylnorflurazon is derived from 1 ppm norflurazon. However, since tolerances established under 40 CFR §180.356 combined norflurazon and desmethylnorflurazon and calculated desmethylnorflurazon "as the stoichiometric equivalent of norflurazon, in or on the commodity" (US EPA, 2012b; eCFR, 2022), 1 ppm of desmethylnorflurazon is considered to be equivalent to 1 ppm norflurazon in this document.

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)
US EPA	1996	R.E.D. Facts of Norflurazon	US EPA, 1996
USGS	1998	Pesticides in Surface and Ground Water of the United States: Summary of Results of the National Water Quality Assessment Program (NAWQA)	USGS, 1998
DPR	2001	Summary of Toxicology Data Norflurazon.	DPR, 2001
US EPA	2001	Norflurazon. HED Risk Assessment for Tolerance Reassessment Eligibility Decision (TRED)	US EPA, 2001
US EPA	2002	Overview of Norflurazon Risk Assessment	US EPA, 2002
US EPA	2008	Risks of Norflurazon Use to Federally Threatened California Red-legged Frog (*Rana aurora draytonii*)	US EPA, 2008
DPR	2009	Guidance for Dietary Exposure	DPR, 2009
US EPA	2010	Pesticide Product Registrations; Conditional Approvals	US EPA, 2010

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Regulatory Agency	Year	Title	Reference(s)
US EPA	2011	Integrated Risk Information System (IRIS) Glossary	US EPA, 2011a
US EPA	2011	Norflurazon Screening Level Usage Analysis (SLUA)	US EPA, 2011b
	2012	BEAD Chemical Profile for Registration Review: Norflurazon (105801)	US EPA, 2012a
US EPA	2012	Norflurazon: Human Health Risk Scoping Document in Support of Registration Review	US EPA, 2012b
US EPA	2012	Norflurazon: Summary of Hazard and Science Policy Council (HASPOC) Meetings of July 12, 2012: Recommendations on the requirement of a subchronic inhalation study and the neurotoxicity screening battery for norflurazon	US EPA, 2012c
US EPA	2014	Dietary Exposure Evaluation Model User's Guide	US EPA, 2014
US EPA	2015	Norflurazon: Data Evaluation Records (DERs) for EDSP Tier 1 Assays	US EPA, 2015a
US EPA	2015	Norflurazon: Weight of Evidence Analysis of Potential Interaction with the Estrogen, Androgen, or Thyroid Pathways (WOE)	US EPA, 2015b
US EPA	2017	Norflurazon. Registration Review. Summary of Analytical Chemistry and Residue Data	US EPA, 2017a
US EPA	2017	Norflurazon: Draft Human Health Risk Assessment in Support of Registration Review	US EPA, 2017b
US EPA	2017	Norflurazon: Summary of Hazard and Science Policy Council (HASPOC) Meeting on August 4, 2016: Recommendations on the Need for an Immunotoxicity Study (870. 7800)	US EPA, 2017c
US EPA	2017	Norflurazon: Summary of Hazard and Science Policy Council (HASPOC) Meeting on June 15, 2017: Recommendations on the Need for Comparative Thyroid Assay	.US EPA, 2017d
US EPA	2017	Registration Review: Preliminary Risk Assessment for Environmental Fate and Ecological Risk for Norflurazon.	US EPA, 2017e
US EPA	2017	Registration Review: Tier 2 Drinking Water Assessment for Norflurazon	US EPA, 2017f
DPR	2018	2018 Annual Statewide Pesticide Use Report Chemical Totals	DPR, 2018
US EPA	2018	2018 Edition of the Drinking Water Standards and Health Advisories Tables	US EPA, 2018a
US EPA	2018	Label Review Manual, Chapter 7: Precautionary Statements	US EPA, 2018b
US EPA	2018	Norflurazon – EFED Response to Public Comments on the Drinking Water Assessment and Preliminary Ecological Risk Assessment in Support of the Registration Review of Norflurazon	US EPA, 2018c
USGS	2018	Health-Based Screening Levels for Evaluating Water-Quality Data	USGS, 2018a
USGS	2018	Health-Based Screening Levels: Updated 2018 Technical Information	USGS, 2018b
US EPA	2019	Norflurazon: Summary of Hazard and Science Policy Council (HASPOC) Meetings on February 7th and March 7th, 2019. Revisit of the Recommendations on the need for Comparative Thyroid Assay. (March 14, 2019)	US EPA, 2019
US EPA	2021	2021 Human Health Benchmarks for Pesticides	US EPA, 2021a
US EPA	2021	D462850 Revised Norflurazon Occupational Handler Calculator	US EPA, 2021b

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
US EPA	2021	Human Health Benchmarks for Pesticides: Updated 2021 Technical Document	US EPA, 2021c
US EPA	2021	Norflurazon (105801) Screening Level Usage Analysis (SLUA) (June 23, 2021)	US EPA, 2021d
DPR	2022	California Code of Regulations (Title 3. Food and Agriculture) Division 6. Pesticides and Pest Control Operations	DPR, 2022a
DPR	2022	California Pesticide Illness Query (CalPIQ)	DPR, 2022b
DPR	2022	Company Address, Name, and Number Search	DPR, 2022c
DPR	2022	Human Health Risk Assessment and Mitigation by Active Ingredient	DPR, 2022d
DPR	2022	Search for Chemical Ingredient by Partial Name, Chemical Code or CAS Number	DPR, 2022e
eCFR	2022	Code of Federal Regulation. §180.356 Norflurazon; tolerances for residues	eCFR, 2022
NIH	2022	National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 33775, Norflurazon	NIH, 2022a
NIH	2022	National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 53708344	NIH, 2022b
OEHHA	2022	The Proposition 65 List	OEHHA, 2022
US EPA	2022	Analysis of Subsurface Metabolism in Groundwater Modeling	US EPA, 2022a
US EPA	2022	CompTox Chemicals Dashboard: Desmethylnorflurazon	US EPA, 2022b
US EPA	2022	CompTox Chemicals Dashboard: Norflurazon	US EPA, 2022c
US EPA	2022	National Primary Drinking Water Regulations	US EPA, 2022d
US EPA	2022	Norflurazon (PC 105801): Use, Usage, and Benefits Information Including Impacts from Potential Mitigation (December 1, 2022)	US EPA, 2022e
US EPA	2022	Norflurazon Proposed Interim Registration Review Decision Case Number 0229	US EPA, 2022f
US EPA	2022	Norflurazon. Updated Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessments in Support of Registration Review	US EPA, 2022g
US EPA	2022	Norflurazon: Addendum to the Preliminary Ecological Risk Assessment for Registration Review (September 21, 2022)	US EPA, 2022h
US EPA	2022	Norflurazon: Revised Human Health Risk Assessment in Support of Registration Review (September 26, 2022)	US EPA, 2022i
US EPA	2022	Norflurazon: Revised Occupational and Residential Exposure and Risk Assessment in Support of the Registration Review (September 22, 2022)	US EPA, 2022j
US EPA	2022	Norflurazon: Tier I Update Review of Human Incidents and Epidemiology for Proposed Interim Decision (PID) (May 9, 2022)	US EPA, 2022k
US EPA	2022	D442228 Appendix D: Norflurazon Spray Drift Exposures and Risks	US EPA, 2022l

DPR: Department of Pesticide Regulation; eCFR: Electronic Code of Federal Regulations; NIH: National Institute of Health; US EPA: United States Environmental Protection Agency; USGS: United States Geological Survey; OEHHA: Office of Environmental Health Hazard Assessment

Summary of Toxicology

Norflurazon has an acute Toxicity Category[1] value of IV for oral, dermal and inhalation toxicities based on their median lethal doses and is neither a skin sensitizer nor an eye or skin irritant (US EPA, 2001; US EPA, 2017b; US EPA, 2022i). US EPA classified norflurazon as a possible human carcinogen (Category C) based on increased incidences in liver adenomas and combined liver adenomas/carcinomas in male mice at the highest tested dose (219 mg/kg/day) (US EPA, 1996; DPR, 2001; US EPA, 2017b; US EPA, 2022i). US EPA concluded that a quantitative cancer risk assessment for norflurazon was not required since presence of benign tumors was observed only in one sex of one species at one dose level and mutagenicity results were negative (DPR, 2001; US EPA, 2017b).

Norflurazon and desmethylnorflurazon are not included on the Proposition 65 (the California Safe Drinking Water and Toxic Enforcement Act of 1986) list of chemicals known to cause cancer, reproductive toxicity, or developmental toxicity (OEHHA, 2022).

Toxicological studies showed that chronic oral treatment of laboratory animals with norflurazon resulted in histopathological changes in kidney and increased thyroid weights in rats, enlarged spleens and nephritis in male mice, enlarged livers, cystic ovaries and pyelonephritis in female mice, and inflammation and other histopathological changes of liver in dogs (US EPA, 2017b; US EPA, 2022i). All of the chronic toxicity studies reported increased liver and kidney weights (US EPA, 2001; US EPA, 2002; US EPA, 2017b). Increased incidences of late abortion, respiratory abnormalities and decreased fetal body weight were observed in a rabbit developmental study (US EPA, 2017b; US EPA, 2022i). There is no evidence of neurotoxicity, immunotoxicity or reproductive toxicity for norflurazon (US EPA, 2017b),

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 twelve reported cases involving exposure to norflurazon alone or in combination with other active ingredients (DPR, 2022b). In the only case associated with exposure to norflurazon alone, skin rash and swelling on the head and neck were observed.

HHA has evaluated all required toxicity data submitted for norflurazon as part of registration in California but has not conducted a human health risk assessment (DPR, 2001). For this evaluation, HHA considered toxicological endpoints and points of departure (PODs) established by US EPA. US EPA did not establish an acute POD for norflurazon but did establish a short-term incidental oral POD. This POD was a no observed adverse effect level (NOAEL) of 30

[1] 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 (US EPA, 2018b).

mg/kg/day and was based on increased incidences of late abortion at the lowest observed adverse effect level (LOAEL) of 60 mg/kg/day in a developmental study in rabbits (US EPA, 2017b; US EPA, 2022i). The NOAEL of 30 mg/kg/day was adopted as the acute POD of norflurazon. This NOAEL was divided by a total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose (aRfD[2]) of 0.30 mg/kg/day. The UF_{TOTAL} included a 10x for interspecies extrapolation (UF_A) and 10x for intraspecies variation (UF_H) (US EPA, 2022i). The chronic POD was a NOAEL of 1.5 mg/kg/day based on liver inflammation and decreased bodyweight in both sexes, and increased food convention indices in female dogs observed at the LOAEL (6.3 mg/kg/day) in a 1-year toxicity study (US EPA, 2022i). The chronic RfD (cRfD) of 0.015 mg/kg/day (all populations) was calculated by dividing the NOAEL by the UF_{TOTAL} of 100 (10x each for interspecies and intraspecies extrapolation) (US EPA, 2022i).

Calculation of DPR Human Health Reference Levels for Norflurazon and Desmethylnorflurazon

An HHRL is the threshold pesticide residue for a maximum water intake that results in the maximum safe oral exposure. HHRLs were calculated using the acute and chronic RfDs for norflurazon as the maximum safe exposure and the acute (95th percentile) and chronic (mean) drinking water intake rates for non-nursing infants as the maximum water intake. Non-nursing infants are the population identified as having the highest consumption of drinking water per kilogram of body weight 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 (US EPA, 2014). HHA uses the 95th 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).

HHA calculated acute and chronic HHRLs for norflurazon in groundwater or drinking water. The results were summarized in Table 2. The lower reference value, the chronic HHRL level of 150 ppb, was selected as the HHRL for residues of norflurazon in groundwater or drinking water and is intended to be used for screening maximum detected residue levels. The same HHRL level

[2] 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 (US EPA, 2011a).

may also be used to screen residues of desmethylnorflurazon alone or a combination of norflurazon and desmethylnorflurazon.

Table 2. Acute and Chronic DPR HHRLs for Norflurazon or Desmethylnorflurazon in Groundwater

Residue	Acute or Chronic	Water Consumption Rates for Non-Nursing Infants[a] (L water/kg BW)	RfD[b] (mg/kg/day)	HHRL[c] (ppb)	US EPA HHBP[d] (ppb)
Norflurazon and/or Desmethylnorflurazon	Acute	0.19	0.30	1579	NA
	Chronic	0.10	0.015	**150**	8.9 (General Population)

[a] 95th percentile water consumption rates for non-nursing infants 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.

[b] RfD: reference dose. Acute and chronic RfDs for norflurazon were established by HHA and US EPA, respectively, as described in the text.

[c] HHRL: human health reference level. HHRL (ppb) = [RfD (mg/kg/day) x 1000 (µg/mg)] / Daily water intake (L/kg/day). Daily water intake is 95th percentile for acute or chronic (mean) water consumption rates for non-nursing infants.

[d] HHBP: human health benchmark for pesticides. An HHBP (ppb) for chronic exposure in general population = [chronic RfD (mg/kg bw/day) x 1000 (µg/mg) x 0.2 RSC] / 0.0338 (L/kg/day) DWI-BW ratio. RSC: relative source contribution, assumed as 20% (US EPA, 2021a). Note: the HHBPs have not yet been updated with the PODs established in the US EPA's recent human health risk assessment (US EPA, 2022i).

The recommended HHRL for screening norflurazon and desmethylnorflurazon residues in drinking water is **bolded**.

Other Reference or Regulatory Levels

Neither norflurazon nor desmethylnorflurazon has an enforceable US EPA Maximum Contaminant Levels (MCLs[3]) or US EPA Health Advisories (HAs[4]) (US EPA, 2018a; US EPA, 2022d). US EPA did not establish an acute Human Health Benchmark for Pesticides (HHBP[5]) for norflurazon but did establish a chronic HHBP (8.9 ppb) (Table 2) (US EPA, 2021a). It should be noted that HHBPs for norflurazon have not been updated to be consistent with the US EPA recently revised human health risk assessment (US EPA, 2022i). Although the chronic HHBP and DPR chronic HHRL are both based on the same chronic PODs, the US EPA chronic HHBP and DPR chronic HHRL differ because they were calculated using different parameters and/or assumptions (*e.g.,* consumption rates and relative source contribution (RSC) factors). The DPR HHRL of 150 ppb is the only reference level that is specifically intended to be used for screening maximum detected residue levels of norflurazon and/or desmethylnorflurazon in groundwater.

Conclusions

HHA calculated Human Health Reference Levels (HHRLs) to be used when norflurazon or desmethylnorflurazon residues are detected in groundwater or drinking water. Residue levels of norflurazon and desmethylnorflurazon, alone or in combination, equal to or less than the DPR HHRL of **150 ppb** in drinking water are not expected to pose a risk to human health, including for sensitive subpopulations. Thus, the highest reported detections of norflurazon and desmethylnorflurazon in groundwater should not be considered as acute or chronic health concerns.

[3] 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/ground-water-and-drinking-water/national-primary-drinking-water-regulations (US EPA, 2022d).

[4] 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 (US EPA, 2018a).

[5] The 2021 HHBPs contained 430 pesticides that currently have no federal drinking water standards. The HHBPs are not legally enforceable federal standards but rather provided by US EPA for pesticides that have no drinking water standards or health advisories (HAs). Available at https://www.epa.gov/system/files/documents/2021-07/hh-benchmarks-technical-document-2021.pdf (US EPA, 2021c).

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Appendix 1: DPR Memo: Potential Health Effects of Norflurazon in Groundwater 10 August 2022 (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 12/1/22*
Environmental Program Manager II
Environmental Monitoring Branch

FROM: Joy Dias *Original Signed by 12/1/22*
Environmental Program Manager I
Environmental Monitoring Branch

DATE: December 1, 2022

SUBJECT: HUMAN HEALTH REFERENCE LEVEL REQUEST FOR NORFLURAZON AND ITS DEGRADATE IN GROUNDWATER

The Environmental Monitoring Branch (EMB) monitors the environment to determine the fate of pesticides, protecting 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) routinely monitors for norflurazon and its degradate, desmethylnorflurazon (DSMN), due to their occurrence in groundwater and norflurazon's status as a 3CCR 6800(a) pesticide. The GWPP also gathers data from all public agencies that report groundwater monitoring data of pesticides and their degradates and enters the data into the Well Inventory Database (WIDB). Norflurazon and DSMN are commonly detected in the same groundwater samples. The highest reported concentration of norflurazon and DSMN are listed in Table 1. The concentration of the parent or degradate also detected in that sample is shown in the footnotes.

EMB requests the assistance of the Human Health Assessment Branch in determining whether these detections pose a significant risk to human health and to provide human health reference levels for norflurazon and DSMN to use for screening detections.

Table 1. Summary of highest reported detections of norflurazon and DSMN from the Well Inventory Database.

Chemical	DPR Chemical Code	CAS Number	Maximum Concentration Reported (ppb)	Year
Norflurazon	2019	27314-13-2	2.48*	2007
DSMN	5890	23576-24-1	1.97**	2017

* DSMN was also detected in this sample at 1.44 ppb
** Norflurazon was also detected in this sample at 0.283 ppb

cc: Carissa Ganapathy, Senior Environmental Scientist (Supervisory)