M E M O R A N D U M

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DATE: June 18, 2025

SUBJECT: HUMAN HEALTH REFERENCE LEVELS FOR INPYRFLUXAM IN SURFACE WATER

On September 20, 2021, the Human Health Assessment Branch (HHA) of the Department of Pesticide Regulation's (DPR) completed a pre-registrational evaluation of a formulated pesticide containing the active ingredient inpyrfluxam that was designated for use in rice crop protection (Track ID 292894). As part of that work, HHA developed Human Health Reference Levels (HHRLs) for inpyrfluxam for DPR's Surface Water Protection Program (SWPP) of the Environmental Monitoring Branch (EMB) to use in evaluating whether anticipated inpyrfluxam residues in drinking water might pose a risk to human health. This memorandum updates the previous HHRLs and reflects HHA's current method of establishing separate HHRLs for maximum and average residue levels for surface water.

Conclusions and Recommendations:

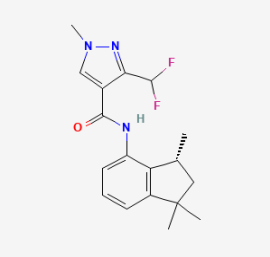
1. HHA calculated Human Health Reference Levels (HHRLs) to be used for detected or model-estimated concentrations of inpyrfluxam in surface water using (1) acute and chronic consumption rates for drinking water from the National Health and Nutrition Examination Survey (NHANES) 2005–2010 database; and (2) toxicological endpoints established by the United States Environmental Protection Agency (US EPA).
2. Inpyrfluxam and its degradates (3-OH-S-2840, 1-COOH-S-2840-A, 1-COOH-S-2840-B, and 1-Keto-S-2840) are residues of concern in drinking water. These chemicals are considered

toxicologically equivalent to inpyrfluxam and should be summated if detected in the same samples.

3. The DPR Acute Surface Water HHRL of inpyrfluxam at 1579 parts per billion (ppb) applies to the evaluation of **maximum** residue levels of inpyrfluxam in surface water. Concentrations of inpyrfluxam equal to or less than 1579 ppb are not expected to pose an acute risk to human health, including for sensitive subpopulations. This is a revision to the previous acute HHRL level of 1542 ppb.
4. The DPR Chronic Surface Water HHRL for inpyrfluxam (520 ppb) is for the evaluation of **average** residue levels in surface water. Average concentrations of inpyrfluxam in surface water equal to or less than 520 ppb are not expected to pose a chronic risk to human health, including for sensitive subpopulations. This is a revision to the previous chronic HHRL level of 3012 ppb.

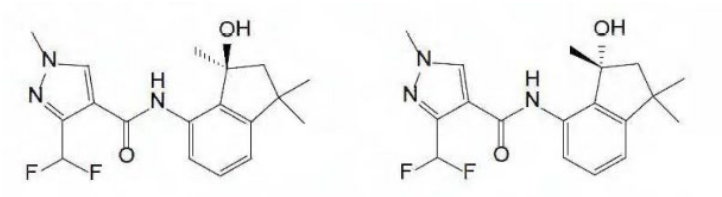
Background

Technical Name: Inpyrfluxam
Chemical Name: 3-(difluoromethyl)-1-methyl-*N*-[(3*R*)-1,1,3-trimethyl-2,3-dihydroinden-4-yl]pyrazole-4-carboxamide
Chemical Abstracts Service Registry Number (CAS #): 1611486-95-3
Molecular Weight: 333.4 g/mol
Chemical Structure:



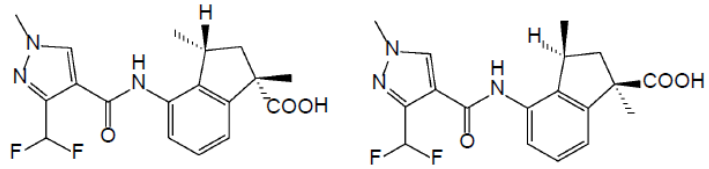
(NIH, 2025)

Technical Name: 3-OH-S-2840
Chemical Name: 3-(Difluoromethyl)-N-[3-hydroxy-(3RS)-1,1,3-trimethyl-2,3-dihydro-1H-inden-4-yl)-1-methyl-IH-pyrazole-4-carboxamide
Chemical Abstracts Service Registry Number (CAS #): NA
Molecular Weight: 349.4 g/mol
Chemical Structure:



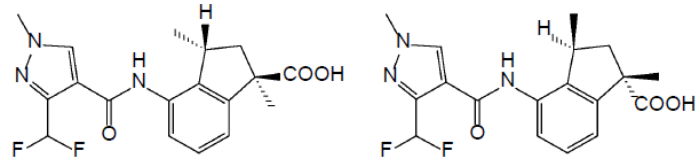
(3'R) (3’S)
(US EPA, 2019a; US EPA, 2020e)

Technical Name: 1-COOH-S-2840-A
Chemical Name: (1RS,3SR)-2,3-dihydro-l,3-dimethyl-4-{[l-methyl-3-(difluoromethyl)-lH-pyrazole-4-ylcarbony]amino}-lH-indene-1-carboxylic acid
Chemical Abstracts Service Registry Number (CAS #): NA
Molecular Weight: 363.4 g/mol
Chemical Structure:



(l'R,3'S) (l'S,3'R)
(US EPA, 2019a; US EPA, 2020e)

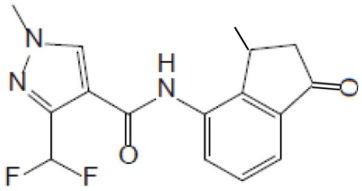
Technical Name: 1-COOH-S-2840-B
Chemical Name: (1RS,3RS)-2,3-dihydro-l,3-dimethyl-4-{[l-methyl-3-(difluoromethyl)-lH-pyrazole-4-ylcarbony]amino}-lH-indene-1-carboxylic acid
Chemical Abstracts Service Registry Number (CAS #): NA
Molecular Weight: 363.4 g/mol
Chemical Structure:



(l'R,3'R) (l'S,3'S)
(US EPA, 2019a; US EPA, 2020e)

Technical Name: 1-Keto-S-2840
Chemical Name: 3-(difluoromethyl)-l-methyl-N-[(3RS)- 3-methyl-l-oxo-2,3-dihydro-lH-inden-4-yl]-lH-pyrazole-4-carboxamide

Chemical Abstracts Service Registry Number (CAS #): NA
Molecular Weight: NA
Chemical Structure:



(US EPA, 2019b)

Inpyrfluxam is a pyrazolecarboxamide fungicide (Group 7 fungicide) acting as a succinate dehydrogenase inhibitor to disrupt the tricarboxylic cycle and mitochondrial electron transport chain in fungi (US EPA, 2020d). It is approved for seed treatment or for broadcast foliar/soil applications to control fungal diseases on many crops (*e.g.*, apples, cereal grains, corn, peanut, rice, sorghum, sugar beet, and vegetables) (US EPA, 2020d). Inpyrfluxam was first registered by US EPA in 2020 and by DPR for use in California in 2021 (DPR, 2025c; US EPA, 2025d). As of June 2025, there are three products actively registered for use in California (DPR, 2025c). Inpyrfluxam is not approved for residential uses (US EPA, 2020d).

Residues of concern in drinking water are the parent inpyrfluxam and its degradates 3-OH-S-2840, 1-COOH-S-2840-A, 1-COOH-S-2840-B, and 1-Keto-S-2840 (US EPA, 2020c). These degradates are considered having similar toxicity to parent and these residues should be summated if detected in the same samples (US EPA, 2019b; US EPA, 2020d; eCFR, 2025). US EPA does not identify that inpyrfluxam has a common mechanism of toxicity with other substances. Thus, cumulative risk assessments are not required (US EPA, 2020d).

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	2000	Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health (2000)	US EPA, 2000
DPR	2009	Guidance for Dietary Exposure Assessment	DPR, 2009
US EPA	2014	Dietary Exposure Evaluation Model User's Guide	US EPA, 2014
US EPA	2015	Human Health Ambient Water Quality Criteria: 2015 Update.	US EPA, 2015

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
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	2019	Analytical Method for S-2399 and Three of its Metabolites 3'-OH-S-2840, 1'-COOH-S-2840A, and 1'-COOH-S-2840-B in soil. Inpyrfluxam (S-2399; PC 090114) MRIDs 49706427/49706090	US EPA, 2019a
US EPA	2019	Drinking Water Assessment for the Proposed Registration of Inpyrfluxam.	US EPA, 2019b
US EPA	2019	Review of Submitted Data Relating to Claims of Mixture Toxicity Associated with Inpyrfluxam.	US EPA, 2019c
DPR	2020	Summary of Toxicology Data Inpyrfluxam	DPR, 2020
US EPA	2020	Inpyrfluxam. Occupational and Residential Exposure Assessment for the Proposed Uses of the New Active Ingredient Inpyrfluxam	US EPA, 2020a
US EPA	2020	Inpyrfluxam: Ecological Hazard Comparison in Support of the Registration Decision	US EPA, 2020b
US EPA	2020	Inpyrfluxam: Revised Acute and Chronic Dietary (Food and Drinking Water) Exposure and Risk Assessment for the New Active Ingredient Inpyrfluxam, for Foliar Application on Apple, Peanut, Soybean, and Sugar Beet; Soil Application on Corn; and Seed Treatment Uses on Canola, Cereal Grains, Legume Vegetables, and Sugar Beet	US EPA, 2020c
US EPA	2020	Inpyrfluxam. Revised Human Health Risk Assessment for the Section 3 Registration Action of the New Active Ingredient, Inpyrfluxam, for Foliar Application on Apple, Peanut, Soybean, and Sugar Beet; Soil Application on Corn; and Seed Treatment Uses on Canola, Cereal Grains, Legume Vegetables, and Sugar Beet	US EPA, 2020d
US EPA	2020	Valent USA Corporation VP-38934	US EPA, 2020e
DPR	2021	California Code of Regulations (Title 3. Food and Agriculture) – Division 6. Pesticides and Pest Control Operations. Chapter 2. Pesticides. Subchapter 1. Pesticide Registration (§6145-6314)	DPR, 2021a
DPR	2021	Evaluating Risk from Exposure to Illegal Pesticides on Fresh Agricultural Commodities.	DPR, 2021b
US EPA	2021	2021 Human Health Benchmarks for Pesticides	US EPA, 2021a
US EPA	2021	Fluopyram: Summary of Hazard and Science Policy Council (HASPOC) Meeting on June 24th, 2021: Recommendations on the Need for a Comparative Thyroid Assay and a 90-day Inhalation Toxicity Study	US EPA, 2021b
US EPA	2021	Human Health Benchmarks for Pesticides: Updated 2021 Technical Document	US EPA, 2021c

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
US EPA	2021	Revised Review of Benefits of Using Inpyrfluxam (A New Fungicide) to Control Fungal Diseases on Many Crops (DP# 444798, PC# 090114, MRID# 50312817)	US EPA, 2021d
DPR	2022	2022 Annual Statewide Pesticide Use Report Chemical Totals	DPR, 2022
US EPA	2023	FINAL Biological Evaluation of Current and Proposed Uses of Inpyrfluxam	US EPA, 2023a
US EPA	2023	Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions	US EPA, 2023b
US EPA	2024	Human Health Water Quality Criteria and Methods for Toxics	US EPA, 2024a
US EPA	2024	Integrated Risk Information System (IRIS) Glossary	US EPA, 2024b
US EPA	2024	National Primary Drinking Water Regulations.	US EPA, 2024c
US EPA	2024	Provisional Peer-Reviewed Toxicity Values (PPRTVs) Assessments	US EPA, 2024d
US EPA	2024	Updated List of Conventional Pesticide Active Ingredients with Adequate Estrogen and Androgen Data for Humans to Inform FFDCA Section 408(p)(6) Determinations	US EPA, 2024e
USGS	2024	Health-Based Screening Levels for Evaluating Water-Quality Data	USGS, 2024
DPR	2025	California Code of Regulations Title 3. Food and Agriculture Division 6. Pesticides and Pest Control Operations	DPR, 2025a
DPR	2025	California Pesticide Illness Query CalPIQ	DPR, 2025b
DPR	2025	CalPEST	DPR, 2025c
DPR	2025	Environmental Monitoring Programs and Projects	DPR, 2025d
eCFR	2025	Code of Federal Regulation. § 180.712 Inpyrfluxam; Tolerances for Residues	eCFR, 2025
OEHHA	2025	The Proposition 65 List.	OEHHA, 2025a
OEHHA	2025	Public Health Goals (PHGs)	OEHHA, 2025b
US EPA	2025	CompTox Chemicals Dashboard: Inpyrfluxam	US EPA, 2025a
US EPA	2025	Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity	US EPA, 2025b
US EPA	2025	Incident Data System (IDS) - All Aggregate Summary Incidents: Inpyrfluxam	US EPA, 2025c
US EPA	2025	Pesticide Chemical Search: Inpyrfluxam	US EPA, 2025d

DPR: Department of Pesticide Regulation; eCFR: online version of Code of Federal Regulation; US EPA: United States Environmental Protection Agency; USGS: United States Geological Survey; OEHHA: Office of Environmental Health Hazard Assessment

Summary of Toxicology

Inpyrfluxam has an acute Toxicity Category[1] value of II for oral, III for dermal and IV for inhalation hazards based on median lethal doses. It is minimally irritating to eyes and negative in dermal irritation tests (Toxicity Category III and IV, respectively). Inpyrfluxam is not a dermal sensitizer (DPR, 2020; US EPA, 2020d). US EPA classified inpyrfluxam as "Not likely to be Carcinogenic to Humans" based on negative results in mutagenicity tests and no evidence of treatment-related increases in tumors in carcinogenicity studies in mice and rats (US EPA, 2020d).

Inpyrfluxam is not 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, 2025a).

Decreased motor activity was noted in an acute neurotoxicity study for inpyrfluxam. Subchronic and chronic toxicity studies show that the target organs for inpyrfluxam are the liver and thyroid gland. Decreased body weights, increased liver weights and liver enzymes, increased incidence of diffuse hepatocellular hypertrophy and thyroid hypertrophy, and/or effects in the ovary and adrenals were observed in rats and dogs. Decreased body weights and food consumption, and liver effects (increased weights, fatty liver, or hepatic hypertrophy) were noted in mice. Incidence of amyloidosis was significantly increased in cervical lymph nodes and glandular stomach in female mice in a chronic toxicity study (DPR, 2020; US EPA, 2020d). Mechanistic studies suggested that hepatic enzyme induction can lead to thyroid hypertrophy through hypothalamus-pituitary-thyroid hormone axis in rats and dogs (DPR, 2020).

HHA has evaluated all required toxicity data submitted as part of registration for inpyrfluxam in California but has not conducted a human health risk assessment (DPR, 2020). For purposes of this evaluation, HHA reviewed relevant regulatory documents (Table 1) and adopted toxicological endpoints established by US EPA (US EPA, 2020c; US EPA, 2020d). US EPA established an acute point of departure (POD[2]) of 30 mg/kg/day for inpyrfluxam that was a no observed adverse effect level (NOAEL) based on reduced motor activity at the lowest observed adverse effect level (LOAEL) of 100 mg/kg/day in an acute neurotoxicity study in rats (US EPA,

[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.

[2] Point of departure (POD) is the dose-response point that marks the beginning of a low-dose extrapolation. A POD can be the lower bound dose for an estimated incidence or from a dose-response model (BMD), or a NOAL/NOAEL. Available at https://www.epa.gov/iris/iris-glossary.

2020c; US EPA, 2020d). This NOAEL was divided by a total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose (aRfD[3]) of 0.30 mg/kg/day. The UF_{TOTAL} is comprised of a factor of 10x for interspecies extrapolation (UF_A) and 10x for intraspecies variation (UF_H) (US EPA, 2020d). HHA also uses this inpyrfluxam aRfD for evaluating risk from illegal residues on fresh produce for the California Pesticide Residue Monitoring Program (DPR, 2021b). The chronic POD was a NOAEL of 26 mg/kg/day based on effects on the thyroid gland (increased organ weight and increased incidences of follicular cell hypertrophy) in P and Fl generations and decreased pup weights in Fl and F2 generations at a LOAEL of 86 mg/kg/day in a 2-generation reproductive toxicity study in rats. This chronic POD was divided by 10x for UF_A and 10x for UF_H to calculate a chronic RfD (cRfD) of 0.26 mg/kg/day (US EPA, 2020d).

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 were calculated using the acute and chronic RfDs for inpyrfluxam 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 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 (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).

Formulae Used to Calculate Acute and Chronic Surface Water HHRLs

$$\text{Acute Surface Water HHRL (ppb)} = \frac{\text{acute RfD}}{\text{acute DWI}} \times 1000$$

$$\text{Chronic Surface Water HHRL (ppb)} = \frac{\text{chronic RfD}}{\text{chronic DWI}} \times 1000 \text{ x RSC}$$

[3] 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.

DWI, drinking water intake, is the 95th percentile (acute) or mean (chronic) water consumption rate for non-nursing infants as described above. Acute and chronic DEEM-FCID results for a residue level of 1 ppm consumption default to the DWI rates by dimensional analysis (acute = 0.194566 L water/kg BW and chronic = 0.099559 L water/kg BW/day) (US EPA, 2014). These DWI values were rounded to two decimal points for the calculation of HHRLs (0.19 and 0.10 L water/kg BW) (Table 2).

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 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%). The RSC is routinely used by regulatory agencies for deriving chronic drinking water screening levels (US EPA, 2000; US EPA, 2015; US EPA, 2024a).

Acute Surface Water Human Health Reference Levels for Inpyrfluxam

DPR Acute Surface Water HHRLs are for screening maximum pesticide residue concentrations in drinking water from a surface water body. As shown in Table 2, the DPR Acute Surface Water HHRL for inpyrfluxam in surface water was **1579** ppb. Maximum residue concentrations of inpyrfluxam in surface water equal to or less than the DPR Acute Surface Water HHRL of 1579 ppb are not expected to pose a risk to human health, including for sensitive subpopulations.

Chronic Surface Water Human Health Reference Levels for Inpyrfluxam

A DPR Chronic Surface Water HHRL applies to the evaluation of average pesticide residue levels in a surface water body. HHA calculated the DPR Chronic Surface Water HHRL of **520** ppb for screening average concentrations of inpyrfluxam in surface water (Table 2). Average residue concentrations of inpyrfluxam in surface water equal to or less than 520 ppb are not expected to pose a chronic risk to human health, including for sensitive subpopulations.

Table 2. DPR Surface Water HHRLs[a] for Inpyrfluxam[b]

Residue	Acute or Chronic	Water Consumption Rates for Non-Nursing Infants (L water/kg BW)	RfD (mg/kg/day)	HHRL (ppb)	US EPA HHBP[c] (ppb)
Inpyrfluxam	Acute (maximum residues)	0.19	0.30	**1579**	2000 (Children)
	Chronic (average residues)	0.10	0.26	**520**	1500 (General population)

BW: body weight; DPR: Department of Pesticide Regulation; HHBP: Human Health Benchmark for Pesticides; HHRL: Human Health Reference Level; L: liter; RfD: reference dose; ppb: parts per billion.

[a] The formulae for HHRL calculation are shown in the text.

[b] Inpyrfluxam's degradates of concern 3-OH-S-2840, 1-COOH-S-2840-A, 1-COOH-S-2840-B, and 1-Keto-S-2840 are considered toxicologically equivalent to inpyrfluxam. These chemicals should be summated if they are detected in the same samples.

[c] 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 (US EPA, 2021a). Acute HHBP for Children = [acute RfD (mg/kg/day) x 1000] / [0.15 (L/kg/day) of drinking water intake-BW ratio]. Chronic HHBP for General Population (ppb) = [chronic RfD (mg/kg/day) x 1000 x 0.2 RSC] / [0.0338 (L/kg/day) of drinking water intake-BW ratio].

The recommended HHRLs for screening inpyrfluxam and its degradates of concern in surface water are **bolded**.

Other Reference or Regulatory Levels for Inpyrfluxam in Drinking Water

DPR considers other reference and regulatory levels for drinking water in the development of HHRLs, especially with regards to maintaining current best practices for dietary and drinking water exposure assessments. Common federal regulatory levels for drinking water include US EPA enforceable Maximum Contaminant Levels (MCLs[4]), non-legally enforceable Health Advisories (HAs[5]), and Human Health Benchmark for Pesticides (HHBP[6]), and United States Geological Survey (USGS) Health-Based Screening Levels (HBSLs[7]). For inpyrfluxam, US EPA issued an acute HHBP of 2000 ppb for children and a chronic HHBP of 1500 ppb for the general population (US EPA, 2021a). Although the same RfDs were used between HHBPs and DPR HHRLs for inpyrfluxam at the acute or chronic levels, their values differ because they were calculated using different parameters/assumptions such as water consumption rates.

Conclusions

HHA calculated Human Health Reference Levels (HHRLs) to be used for inpyrfluxam in drinking water from surface water sources. Maximum residue concentrations of inpyrfluxam equal to or less than the DPR Acute Surface Water HHRL of 1579 ppb, or average residue concentrations equal to or less than the DPR Chronic Surface Water HHRL of 520 ppb in surface water, are not expected to pose a risk to human health, including for sensitive subpopulations. Inpyrfluxam and its degradates of concern in drinking water (3-OH-S-2840, 1-COOH-S-2840-A, 1-COOH-S-2840-B, and 1-Keto-S-2840) are considered toxicologically equivalent and are summated if they are detected in the same sample. These inpyrfluxam HHRLs supersede the previously issued acute HHRL of 1542 ppb and chronic HHRL of 3012 ppb.

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[4] 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.

[5] 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.

[6] 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.

[7] 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/.

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