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MEMORANDUM

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VIA: Shelley DuTeaux, PhD MPH, Chief
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DATE: February 20, 2024

SUBJECT: HUMAN HEALTH REFERENCE LEVELS FOR HEXAZINONE IN
GROUNDWATER

On December 19, 2023, the Department of Pesticide Regulation's (DPR) Human Health Assessment Branch (HHA) was requested by the Environmental Monitoring Branch (EMB) to provide Human Health Reference Levels (HHRLs) for screening detections of hexazinone and/or its degradation products in groundwater (see request, Appendix 1). This memorandum is in response to the request.

Conclusions and Recommendations:

1. HHA calculated Human Health Reference Levels (HHRLs) to be used for screening detections of hexazinone and its degradates in groundwater 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. Hexazinone and its degradates of concern in groundwater, G3170, A, A-1, B, C, D, 1, and 2, are considered to have equivalent toxicity and should be summed when they are detected in the same sample.
3. The DPR HHRL for hexazinone is 500 parts-per-billion (ppb). Maximum residue concentrations of hexazinone and its degradates equal to or less than 500 ppb in groundwater are not expected to pose a risk to human health, including for sensitive subpopulations.

Background

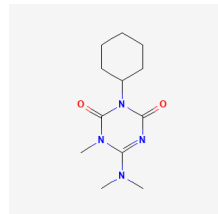
Technical Name: Hexazinone

Chemical Name: 3-cyclohexyl-6-(dimethylamino)-1-methyl-1,3,5-triazine-2,4-dione

Chemical Abstracts Service Registry Number (CAS #): 51235-04-2

Molecular Weight: 252.31 g/mol

Chemical Structure:



(NIH, 2023)

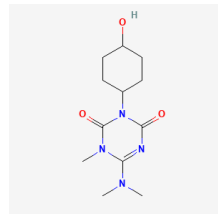
Technical Name: A (T3937)

Chemical Name: 6-(dimethylamino)-3-(4-hydroxycyclohexyl)-1-methyl-1,3,5-triazine-2,4-dione

CAS #: 72576-13-7

Molecular Weight: 268.31 g/mol

Chemical Structure:



(NIH, 2024a)

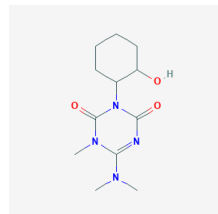
Technical Name: A-1 (G3453)

Chemical Name: 6-(dimethylamino)-3-(2-hydroxycyclohexyl)-1-methyl-1,3,5-triazine-2,4-dione

CAS #: Not Applicable (N/A)

Molecular Weight: 268.31 g/mol

Chemical Structure:



(NIH, 2024e)

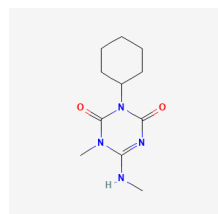
Technical Name: B (A3928)

Chemical Name: 3-cyclohexyl-1-methyl-6-(methylamino)-1,3,5-triazine-2,4-dione

CAS #: 56611-54-2

Molecular Weight: 238.29 g/mol

Chemical Structure:



(NIH, 2024d)

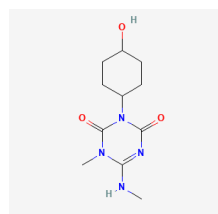
Technical Name: C

Chemical Name: 3-(4-hydroxycyclohexyl)-1-methyl-6-(methylamino)-1,3,5-triazine-2,4-dione

CAS #: 72585-88-7

Molecular Weight: 254.29 g/mol

Chemical Structure:



(NIH, 2024b)

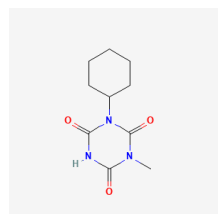
Technical Name: D (B2838)

Chemical Name: 1-cyclohexyl-3-methyl-1,3,5-triazinane-2,4,6-trione

CAS #: 30243-77-7

Molecular Weight: 225.24 g/mol

Chemical Structure:



(NIH, 2024c)

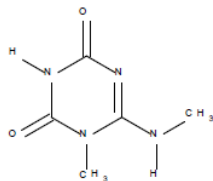
Technical Name: G3170

Chemical Name: 1-Methyl-6-(methylamino)-1,3,5-triazine-2,4-dione

CAS #: N/A

Molecular Weight: 156.14 g/mol

Chemical Structure:



(US EPA, 2015a)

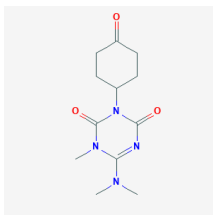
Technical Name: 1 (JS472)

Chemical Name: 6-(dimethylamino)-1-methyl-3-(4-oxocyclohexyl)-1,3,5-triazine-2,4-dione

CAS #: N/A

Molecular Weight: 266.3 g/mol

Chemical Structure:



(NIH, 2024f)

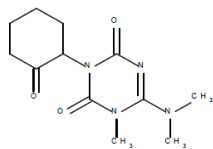
Technical Name: 2 (JT677)

Chemical Name: 6-(dimethylamino)-1-methyl-3-(2-oxocyclohexyl)-1,3,5-triazine-2,4-dione

CAS #: N/A

Molecular Weight: 266.3 g/mol

Chemical Structure:



(US EPA, 2015a)

Basic Information

Hexazinone is a triazinone broad spectrum systemic pre- and post-emergent herbicide used to control annual and perennial broadleaf weeds, some grasses, and some woody species (US EPA, 2016b). It is registered for use on agricultural field crops (*e.g.*, alfalfa, sugarcane, pineapple, and blueberries), pasture, rangeland, and non-food crop areas (*e.g.*, forestry, Christmas trees, etc.), but not for residential uses (US EPA, 2015b; US EPA, 2016a). Hexazinone's mode of action is via inhibition of photosystem II of photosynthesis, which mediates foliar chlorosis and necrosis

(US EPA, 2016b). Hexazinone was first registered by the US Environmental Protection Agency (US EPA) in 1975 for the control of weeds in non-cropland areas (US EPA, 1994). Between 2010 and 2014, hexazinone was applied to approximately 526,000 acres of agriculture annually in the US with maximum single application rates of 1.5 to 4 pounds of active ingredient per acre (US EPA, 2016b). Hexazinone was first registered in California in 1981, and as of December 2023 there are nine active registrations (DPR, 2023). According to the most currently available data from the DPR’s Pesticide Use Reporting (PUR) database, 59,840 pounds of hexazinone active ingredient were used in 1,134 California agricultural applications in 2021(DPR, 2021).

In addition to hexazinone, degradates of concern in groundwater include G3170, A, A-1, B, C, D, 1, and 2 (US EPA, 2002b; US EPA, 2002a; US EPA, 2015b). The US EPA Health Effects Division’s (HED) Metabolism Assessment Review Committee (MARC) considers the parent compound hexazinone and its degradates A, A-1, B, C, D, 1, and 2 to share similar toxicity based on structural similarities (US EPA, 2002b). Although G3170 is not structurally similar to hexazinone, it is also evaluated as a hexazinone equivalent in the risk assessment; thus, hexazinone and all eight degradates should be summed if they are detected in the same sample (US EPA, 2002a; US EPA, 2002b; US EPA, 2002d).

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). A comprehensive systematic review was beyond the scope of the request.

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference
US EPA	1994	Reregistration Eligibility Decision (RED) Hexazinone	US EPA (1994)
DPR	2000	Summary of Toxicology Data for Hexazinone	DPR (2000)
US EPA	2002	Overview of Hexazinone Risk Assessment	US EPA (2002a)
US EPA	2002	Revised: HED Chapter for the Hexazinone Tolerance Reassessment Eligibility Decision PC Code 107201. Case 0266. DP Barcode D275621	US EPA (2002b)
US EPA	2002	Subject: 107201: The Revised Toxicology Chapter for the TRED for Hexazinone	US EPA (2002c)
US EPA	2002	Tier I Estimated Environmental Concentrations of Hexazinone, for use in Human Health Risk Assessment	US EPA (2002d)
DPR	2003	Summary of Results for Fiscal Year 2002/03 Ground Water Protection List Monitoring for Hexazinone and Three of its Degradates	DPR (2003)
DPR	2009	Guidance for Dietary Exposure Assessment	DPR (2009)

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference
US EPA	2010	Hexazinone Summary Document Registration Review: Initial Docket	US EPA (2010a)
US EPA	2010	Hexazinone: Revised Registration Review Scoping Document for Human Health Risk Assessments	US EPA (2010b)
US EPA	2011	Integrated Risk Information System (IRIS) Glossary	US EPA (2011)
US EPA	2014	Dietary Exposure Evaluation Model User's Guide	US EPA (2014)
US EPA	2015	Estimated Drinking Waters Concentrations for the Registration Review of Hexazinone (PC Code 107201; DP Barcode 0424532)	US EPA (2015a)
US EPA	2015	Hexazinone: Draft Human Health Risk Assessment for Registration Review	US EPA (2015b)
US EPA	2015	Hexazinone: Tier I Update Review of Human Incidents/Epidemiology for Draft Risk Assessment	US EPA (2015c)
US EPA	2015	Human Health Ambient Water Quality Criteria: 2015 Update	US EPA (2015d)
US EPA	2016	Hexazinone Proposed Interim Registration Review Decision Case Number 0266	US EPA (2016a)
US EPA	2016	Hexazinone Usage and Benefits Information (PC # 107201)	US EPA (2016b)
US EPA	2018	2018 Edition of the Drinking Water Standards and Health Advisories Tables	US EPA (2018a)
US EPA	2018	Amendment to Hexazinone Interim Registration Review Decision, Case Number 0266	US EPA (2018b)
US EPA	2018	Label Review Manual, Chapter 7: Precautionary Statements	US EPA (2018c)
USGS	2018	Health-Based Screening Levels for Evaluating Water-Quality Data	USGS (2018)
US EPA	2019	Development of the Proposed Unregulated Contaminant Monitoring Rule for the Fifth Monitoring Cycle (UCMR 5): Meeting Summary	US EPA (2019)
DPR	2021	2021 Annual Statewide Pesticide Use Report Chemical Totals	DPR (2021)
US EPA	2021	2021 Human Health Benchmarks for Pesticides	US EPA (2021a)
US EPA	2021	Human Health Benchmarks for Pesticides: Updated 2021 Technical Document	US EPA (2021b)
US EPA	2022	Technical Support Document for the Final Fifth Contaminant Candidate List (CCL 5) - Contaminant Information Sheets	US EPA (2022)
DPR	2023	Search for Chemical Ingredient by Partial Name, Chemical Code or CAS Number	DPR (2023)
eCFR	2023	Code of Federal Regulation. § 180.396 Hexazinone; tolerances for residues	eCFR (2023)
NIH	2023	National Center for Biotechnology Information	NIH (2023)
OEHHA	2023	The Proposition 65 List	OEHHA (2023)
US EPA	2023	List of Conventional Registration Review Chemicals for Which an FFDCA Section 408(p)(6) Determination is Needed	US EPA (2023)
DPR	2024	California Pesticide Illness Query (CalPIQ)	DPR (2024)
NIH	2024	PubChem Compound Summary	NIH (2024a)
US EPA	2024	Human Health Water Quality Criteria and Methods for Toxics	US EPA (2024)

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference
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

Hexazinone is designated as Toxicity Category¹ III for acute oral and inhalation hazards and Toxicity Category IV for dermal hazards based on median lethal doses (US EPA, 2015b). It causes severe primary eye irritation (Toxicity Category I) (US EPA, 2015b). Hexazinone causes mild skin irritation (Toxicity Category IV) but is not considered a skin sensitizer (US EPA, 2015b). US EPA classified hexazinone as a “Group D chemical, not classifiable as to human carcinogenicity” based on insufficient or lack of evidence for carcinogenicity in rodent studies or evidence of mutagenicity in genotoxicity studies (US EPA, 2015b). Hexazinone is not included on the Proposition 65 (California Safe Drinking Water and Toxic Enforcement Act of 1986) list for chemicals known to cause cancer, reproductive toxicity, or developmental toxicity (OEHHA, 2023).

Decreased body weights and liver toxicity were the most common effects observed in dogs, rats, and mice following repeated exposures to hexazinone (US EPA, 2015b). In developmental and reproductive toxicity studies, fetal and pup effects included kidneys with no papillae and misaligned sternbrae in rats, and weight decrements in rabbits and rats (US EPA, 2015b). The treatment related effects on fetuses or pups only occurred at doses of hexazinone that were also toxic to the mothers. The toxicological database did not show evidence that hexazinone causes neurotoxicity (US EPA, 2015b).

DPR’s Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries reported in California from 1992 to 2019 (the most recent data available). There were three reported cases pertaining to hexazinone exposure alone or in combination with other pesticides. In the single case associated with hexazinone-only exposure, a field worker who disced an orchard adjacent to a treated field reported swollen lower eyelids, red and swollen eyes, rash on the forehead and abdomen, disorientation, swollen throat and hands, a strange taste, and disorientation (DPR, 2024).

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).

While HHA has evaluated all required toxicity data submitted for hexazinone for registration of products in California, a risk assessment was not conducted (DPR, 2000). Thus, HHA adopted toxicological endpoints and points of departure (PODs) for hexazinone established by US EPA (US EPA, 2015b). US EPA's acute POD was a no observed adverse effect level (NOAEL) of 125 mg/kg/day based on reduced motor activity in both sexes and decreased body temperature and functional observational battery (FOB) findings in females noted at the lowest observed adverse effect level (LOAEL) of 500 mg/kg/day in an acute neurotoxicity study in rats (US EPA, 2015b). The NOAEL was divided by a default total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose (aRfD²) of 1.25 mg/kg/day (US EPA, 2015b). The UF_{TOTAL} is comprised of 10x to account for interspecies sensitivity (UF_A) and 10x to account for intraspecies (human) variability (UF_H) (US EPA, 2015b). US EPA's chronic POD was a NOAEL of 5 mg/kg/day based on decreased body weights and hepatotoxicity (microscopic lesions and alterations in clinical chemistry values) observed at the LOAEL of 38 mg/kg/day in a one-year oral toxicity study in dogs (US EPA, 2015b). The chronic POD was also divided by a UF_{TOTAL} of 100 (10x each for interspecies and intraspecies extrapolation) to calculate a chronic RfD (cRfD) of 0.05 mg/kg/day (US EPA, 2015b).

Calculation of Human Health Reference Levels (HHRLs) for Hexazinone

An HHRL is the threshold pesticide residue level for a maximum water intake that results in the maximum safe oral exposure. HHRLs were calculated using the acute and chronic RfDs for hexazinone as the maximum safe exposure and the 95th percentile of acute 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). 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 exposure level 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).

² A reference dose (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, 2011).

HHA calculated an acute- and a chronic-HHRL of 6,579 ppb and 500 ppb, respectively, for hexazinone in groundwater (Table 2). The lower reference value, the chronic HHRL level of **500 ppb**, was selected as the DPR HHRL for screening concentrations of hexazinone and its degradates of concern in drinking water. Maximum residue concentrations of hexazinone and/or its degradates in drinking water equal to or less than the DPR HHRL screening level of 500 ppb are not expected to pose a risk to human health, including for sensitive subpopulations.

Other Reference or Regulatory Levels for Hexazinone in Drinking Water

DPR considers other reference and regulatory levels for drinking water in the development of HHRLs, especially with regards to best practices in dietary and drinking water exposure assessment. Common federal reference levels for drinking water include US EPA enforceable Maximum Contaminant Levels (MCLs³), non-legally enforceable Health Advisories (HAs⁴) and Human Health Benchmark for Pesticides (HHBP⁵), and non-legally enforceable United States Geological Survey (USGS) Health-Based Screening Levels (HBSLs⁶). For hexazinone, US EPA issued a one- and ten-day HA of 3,000 and 2,000 ppb, respectively, which are expected to be protective for a 10-kg child consuming 1 liter of water per day (US EPA, 2018a; US EPA, 2021a). Other HAs include a Drinking Water Equivalent Level (DWEL) of 2,000 ppb and a non-carcinogenic lifetime HA (NCHA) exposure level of 400 ppb (US EPA, 2018a). DWELs apply to situations where 100% of the residue intake is assumed to be from water sources. In contrast, NCHA exposure levels incorporate a relative source contribution (RSC) factor of 0.2, assuming that the exposure from water sources will be 20% of the total exposure while other intakes will make up the remainder (80%). USGS's non-cancer HBSL for hexazinone was 300 ppb (USGS, 2018). The DPR HHRL for hexazinone differed from US EPA's HAs and USGS's HBSL because they were calculated using different parameters/assumptions such as water consumption

³ 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> (US EPA, 2018a).

⁴ 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> (US EPA, 2018a).

⁵ 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> (US EPA, 2021b).

⁶ 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/> (USGS, 2018).

rates, RfDs, and RSC factors. The DPR HHRL of 500 ppb is the only reference level that is specifically intended to be used for screening maximum detected residue levels of hexazinone in groundwater.

Table 2. DPR HHRLs^a for Hexazinone^b

Residue	Acute or Chronic	Consumption Rates for Non-Nursing Infants ^c (L water/kg BW)	RfD ^d (mg/kg/day)	HHRL (ppb)	US EPA Health Advisories ^e		
					1-Day/10-Day ^e (10-kg Child) (ppb)	DWEL ^e (ppb)	NCHA ^e (ppb)
Hexazinone	Acute	0.19	1.25	6,579	3,000	2,000	400
	Chronic	0.10	0.05	500			

BW: bodyweight; DWEL: Drinking Water Equivalent Level; HHRL: Human Health Reference Level; L: liter; NCHA: non-carcinogenic lifetime health advisory; RfD: reference dose; ppb: parts-per-billion

^a DPR HHRLs (ppb) for screening maximum pesticide residue levels were calculated as $[RfD (mg/kg/day) \times 1000] / [Daily\ water\ intake (L/kg/day)]$. Daily water intake is 95th percentile for acute or chronic (mean) water consumption rates for non-nursing infants (see Note c).

^b Hexazinone’s eight degradates of concern (A, A-1, B, C, D, G3170, 1, and 2) are considered equivalent to hexazinone.

^c 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.

^d Acute and chronic RfDs (mg/kg/day) were established by US EPA (2015b) as described in the text.

^e US EPA Health Advisories (HAs) are not legally enforceable Federal standards. HAs serve as a technical guidance to assist Federal, State, and local officials (US EPA, 2018a). 1-Day and 10-day parameters are concentrations intended to protect a 10-kg child consuming 1 liter of water per day for up to one day (1-day) and 10 days (10-day) exposure, respectively. A DWEL is a drinking water lifetime maximum noncarcinogenic safe exposure level assuming 100% exposure from that medium. A noncancer lifetime health advisory (NCHA) incorporates a relative source contribution (RSC) factor, assuming that the exposure from water sources will be 20% of the total exposure while other intakes will make up the remainder (80%).

The recommended HHRL for screening residue concentrations of hexazinone and its degradates of concern in drinking water is **500**.

Conclusions

HHA calculated Human Health Reference Levels (HHRLs) to be used when hexazinone and/or its eight degradates of concern (A, A-1, B, C, D, G3170, 1, and 2) are detected in groundwater. Maximum concentrations of these residues, individually or in summation if detected in the same sample, equal to or less than the DPR HHRL of **500 ppb** are not expected to pose a risk to human health, including for sensitive subpopulations.

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Minh Pham
February 20, 2024
Page 17

Appendix

**Appendix 1. DPR Memo: Potential Health Effects of Hexazinone in Groundwater
19 December 2023 (1 page)**



Julie Henderson
Director

MEMORANDUM

Yana Garcia
Secretary for
Environmental Protection

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

VIA: Minh Pham *Original Signed by A. Main for M. Pham 12/19/23*
Environmental Program Manager II
Environmental Monitoring Branch

FROM: Joy Dias *Original Signed by 12/19/23*
Environmental Program Manager I
Environmental Monitoring Branch

DATE: December 19, 2023

SUBJECT: HUMAN HEALTH REFERENCE LEVEL REQUEST FOR HEXAZINONE IN
GROUNDWATER

The Environmental Monitoring Branch (EMB) monitors the environment to determine the fate of pesticides and protects 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 hexazinone due to its occurrence in groundwater and status as a 3CCR 6800(b) 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).

To determine whether detections of hexazinone or any of its degradation products pose a significant risk to human health, EMB requests that the Human Health Assessment Branch provide a human health reference level to use for screening detections in groundwater.

Table 1. Summary information for hexazinone.

Chemical	DPR Chemical Code	CAS Number
Hexazinone	1871	51235-04-2

cc: Carissa Ganapathy, Senior Environmental Scientist (Supervisory)