M E M O R A N D U M

TO: Minh Pham
Environmental Program Manager II
Environmental Monitoring Branch

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

FROM: Brandon M. Brown, PhD, Staff Toxicologist
Pete Lohstroh, PhD, Senior Toxicologist
Toxicology and Dose Response Assessment Section

Svetlana Koshlukova, PhD, Senior Toxicologist
Risk Assessment Section

DATE: December 18, 2023

SUBJECT: RISKS FROM HUMAN EXPOSURE TO PROMETON RESIDUES IN GROUNDWATER

On July 26, 2023, the Department of Pesticide Regulation's (DPR) Human Health Assessment (HHA) Branch was notified by the Environmental Monitoring (EM) Branch that the Groundwater Protection Program (GWPP) detected prometon residues in wells in California. The highest concentration of 5.9 ppb was detected in a domestic well in 1986. The highest concentration detected between 2000 and 2021 was 0.151 ppb. EM requested that HHA determine if there is a health concern for individuals using these wells as a source of drinking water (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 for detections of prometon residues 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).

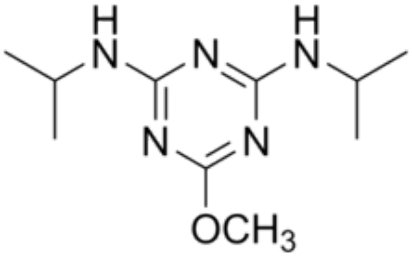
2. Maximum residue levels of prometon equal to or less than the DPR HHRL of 263 parts-per-billion (ppb) in drinking water are not expected to pose a risk to human health, including for sensitive subpopulations. Prometon is a triazine herbicide but since it does not share the common mechanism of toxicity with the other chlorotriazines (e.g., atrazine,

simazine, propazine, etc.), this HHRL should be used for prometon residues alone and should not be summed with chlorotriazine residues.

3. Based on a comparison to the DPR HHRL, the highest measured residue level in groundwater (5.9 ppb) does not pose a health risk to humans.

Background

Technical Name: Prometon
Chemical Name: 6-methoxy-2-*N*,4-*N*-di(propan-2-yl)-1,3,5-triazine-2,4-diamine (NIH, 2023) or 6-methoxy-N,N′-bis(1-methylethyl)-1,3,5-triazine-2,4-diamine (USEPA, 2008)
Chemical Abstracts Service Registry Number (CASRN): 1610-18-0 (USEPA, 2008; NIH, 2023)
Chemical Structure:



Prometon is a triazine herbicide used to control annual and perennial broad-leaf weeds, brush, and grass in non-agricultural areas on industrial sites, on non-crop areas on farms, and under asphalt (USEPA, 2008; USEPA, 2017b). It was first registered in the United States in May of 1959 (USEPA, 2008). Prometon was first registered in California in 1981 and there are currently three products with active registrations (DPR, 2023). Currently, there are no food or feed uses in the US (USEPA, 2017b). While metabolites of prometon have shown to have toxicity similar to the parent, prometon is the only residue of concern based on "limited degradation under environmental conditions" (USEPA, 2017b).

Review of Regulatory Documents

As part of this evaluation, pertinent regulatory documents were reviewed to ensure that the most scientifically supportable toxicological data were used in the evaluation (summarized in Table 1, below). A comprehensive systematic review was beyond the scope of this evaluation.

Table 1. Review of Regulatory Documents

Agency	Year	Title	Reference(s)
DPR	1989	Summary of Toxicology Data Prometon	(DPR, 1989)
US EPA	2006	Triazine Cumulative Risk Assessment	(USEPA, 2006)

Table 1. Review of Regulatory Documents

Agency	Year	Title	Reference(s)
US EPA	2008	Reregistration Eligibility Decision for Prometon	(USEPA, 2008)
US EPA	2017	Prometon. Human Health Draft Risk Assessment in Support of Registration	(USEPA, 2017b)
US EPA	2017	Prometon. Chronic Dietary (Drinking Water Only) Exposure and Risk Assessment for the Registration Review Draft Risk Assessment	(USEPA, 2017a)
USGS	2018	Health-Based Screening Levels for Evaluating Water-Quality Data	(USGS, 2018)
US EPA	2018	Drinking Water Standards and Health Advisories Tables	(USEPA, 2018)
US EPA	2021	Human Health Benchmarks for Pesticides	(USEPA, 2021)
DPR	2022	California Pesticide Illness Query (CalPIQ)	(DPR, 2022)
OEHHA	2023	Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986	(OEHHA, 2023)
DPR	2023	DPR's Chemical/Product Database Queries	(DPR, 2023)
NIH	2023	PubChem Open Chemistry Database, Prometon	(NIH, 2023)

Summary of Toxicology

Prometon is classified as Toxicity Category III[a] for acute oral and dermal hazards based on the median lethal doses, and Toxicity Category II for inhalation based on its median lethal concentration (USEPA, 2008). It is a mild irritant to the eyes (Toxicity Category III), but it is not a dermal irritant or dermal sensitizer (Toxicity Category IV). Prometon is not considered a carcinogen, with the US EPA classifying it as "not likely to be carcinogenic to humans" (USEPA, 2008).

Prometon 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, 2023).

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 12 reported cases involving exposure to prometon, six of which were from prometon alone (DPR, 2022). Of the cases where prometon was the sole cause of pesticide-related illness,

[a] 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. https://www.epa.gov/sites/production/files/2018-04/documents/chap-07-mar-2018.pdf

individuals experienced abdominal cramps, globus or chocking sensation, vomiting, eye irritation, headache, dizziness, nausea, sweating, tremors, chills, and weakness.

Decreased body weight was the principal effect observed after repeated exposures to prometon in rat, rabbit, mouse and dog. Mydriasis, ptosis tremors and ataxia were seen in chronic studies in dogs. While prometon is a triazine herbicide, it was not included in the common mechanism group with other chlorotriazines (e.g. atrazine, simazine and propazine) (USEPA, 2017b). US EPA suggested that this could be due to structural differences since prometon does not have a chlorine atom on the triazine ring, unlike atrazine, simazine and propazine.

HHA has evaluated the required toxicity data submitted for prometon as part of registration in California but has not conducted a human health risk assessment (DPR, 1989). 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 prometon but did establish a short-term incidental oral POD. This POD was a no observed adverse effect level (NOAEL) of 5 mg/kg/day from a chronic study in dogs (USEPA, 2017b). It was based on emesis and body weight decreases observed at the lowest observed adverse effect level (LOAEL) of 24.5 mg/kg/day in a chronic study in dogs. The NOAEL of 5 mg/kg/day was adopted as the acute POD of prometon. This NOAEL was divided by a total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose[b] (aRfD) for prometon of 0.05 mg/kg/day. The UF_{TOTAL} included 10x for interspecies extrapolation (UF_A) and 10x for intraspecies variation (UF_H). The chronic POD was a NOAEL of 5 mg/kg/day based on emesis and body weight decline observed at the LOELs ranging from 20 to 35.08 mg/kg/day in three co-critical studies, a chronic study in dogs, a chronic study in rats and a reproductive toxicity study in rats (USEPA, 2008; USEPA, 2017a; USEPA, 2017b). The chronic RfD (cRfD) of 0.05 mg/kg/day was calculated by dividing the NOAEL by the UF_{TOTAL} of 100 as described above.

Calculation of DPR Human Health Reference Levels for Prometon

An HHRL is the threshold pesticide residue for a maximum water intake that results in the maximum safe oral exposure. The reference levels were calculated using the acute and chronic RfDs for prometon 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-

[b] 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 (USEPA 2011. Integrated Risk Information System (IRIS) Glossary. https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do;jsessionid=VlwqcwYyLhUo1oDvgiO0TvQRBc0DnFfnaT0N8nvQPdtRKQaPCtCF!1236830639?details=&vocabName=IRIS%20Glossary&filterTerm=reference%20dose&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=reference%20dose&filterMatchCriteria=Contains.https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?details=&vocabName=IRIS%20Glossary)

nursing infants are the population identified as having the highest consumption of drinking water among the standard populations that HHA evaluates, including the general US population and sensitive subpopulations such as infants, children aged 1 – 2, and women of childbearing age (13 – 49 years old). 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 (USEPA, 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).

Human Health Reference Levels for Prometon

The HHRLs for prometon in drinking water are summarized below (Table 2). The lowest reference value (acute level 263 ppb) was selected as the HHRL for residues of prometon in groundwater and is intended to be used for screening maximum detected residue level.

Other Reference or Regulatory Levels for Drinking Water

US EPA established Health Advisories (HAs[c]) (1-day, 10-day, and lifetime exposure set at 200, 200, and 400 ppb, respectively) and a Drinking Water Equivalent Level (DWEL[d]) of 2000 ppb for prometon (USEPA, 2018). Additionally, Health-Based Screening Levels (HBSL[e]) database maintained by the US Geological Survey (USGS) included a noncancer HBSL of 300 ppb for prometon (USGS, 2018). No other screening levels, including Maximum Contaminant Levels

[c] 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. USEPA. 2018. Drinking Water Standards and Health Advisories Tables. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf.

[d] A DWEL is a drinking water lifetime maximum noncarcinogenic safe exposure level when assuming 100% exposure from that medium. DWEL is a parameter of Health Advisories (HAs). An HA, not a legally enforceable Federal standard, serves as a technical guidance to assist Federal, State, and local officials" Available at https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf. Ibid.

[e] 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. Health-Based Screening Levels for Evaluating Water-Quality Data. https://water.usgs.gov/water-resources/hbsl/.

(MCLs[f]) or Human Health Benchmark for Pesticides (HHBPs[g]), were issued for prometon. The US EPA and USGS reference levels for prometon differ from DPR HHRL because they were calculated using different parameters/assumptions. The DPR HHRL of 263 ppb is the only reference level that is specifically intended to be used for screening maximum detected residue levels of prometon in groundwater.

Table 2. DPR HHRLs for Prometon

Acute or Chronic	Consumption for Non-Nursing Infants[a] kg water/kg BW	RfD[b] mg/kg/day	Human Health Reference Levels[c] (ppb)	DWEL[d] (ppb)
Acute	0.19	0.05	**263**	NA
Chronic	0.10	0.05	502	2000

[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] Incidental oral and chronic RfDs for prometon were established by US EPA.
[c]The DPR HHRLs (ppb) for screening maximum pesticide residue levels were calculated as [RfD (mg/kg/day) x 1000] / [Daily water intake]. Daily water intake is 95th percentile for acute or chronic (mean) water consumption rates for non-nursing infants (see Note a).
[d] A DWEL is a drinking water lifetime maximum noncarcinogenic safe exposure level assuming 100% exposure from that medium. A noncancer lifetime (NCLT) incorporates a relative source contribution (RSC) factor above DWEL, 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 levels of prometon in drinking water is **bolded**.

[f] 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 USEPA. 2018. Drinking Water Standards and Health Advisories Tables. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf..

[g] 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 USEPA. 2021. Human Health Benchmarks for Pesticides. https://ordspub.epa.gov/ords/pesticides/f?p=HHBP:home.

Conclusions

HHA calculated Human Health Reference Levels (HHRLs) to be used when prometon residues are detected in groundwater. Prometon is a triazine herbicide but since it does not share the common mechanism of toxicity with the other chlorotriazines (e.g., atrazine, simazine, propazine, etc.), this HHRL should be used for prometon residues alone and should not be summed with chlorotriazine residues. Maximum residue levels of prometon equal to or less than the DPR HHRL of **263** ppb are not expected to pose a risk to human health, including for sensitive subpopulations.

Brandon Brown

Brandon M. Brown, PhD
Staff Toxicologist, Toxicology and Dose Response Assessment Section

Svetlana Koshlukova

Svetlana Koshlukova, PhD
Senior Toxicologist, Risk Assessment Section

Peter Lohstroh

Peter N. Lohstroh, PhD
Senior Toxicologist, Toxicology and Dose Response Assessment Section

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USEPA. 2017b. Prometon. Human Health Draft Risk Assessment in Support of Registration. https://www.regulations.gov/document/EPA-HQ-OPP-2013-0068-0019.

USEPA. 2018. Drinking Water Standards and Health Advisories Tables. https://www.epa.gov/system/files/documents/2022-01/dwtable2018.pdf.

USEPA. 2021. Human Health Benchmarks for Pesticides. https://ordspub.epa.gov/ords/pesticides/f?p=HHBP:home.

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Appendices

Appendix 1. DPR Memo: Human Health Reference Level Request for Prometon in Groundwater 26 July 2023 (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
Environmental Program Manager II
Environmental Monitoring Branch

FROM: Joy Dias
Environmental Program Manager I
Environmental Monitoring Branch

Original Signed By C. Ganapathy 7/26/23

DATE: July 26, 2023

SUBJECT: HUMAN HEALTH REFERENCE LEVEL REQUEST FOR PROMETON 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 prometon due to its occurrence in groundwater and 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). Table 1 lists the highest concentration of prometon detected in a domestic drinking water well from the WIDB. The footnote lists the highest concentration detected between 2000 and 2021.

EMB requests the assistance of the Human Health Assessment Branch (HHA) in determining whether the highest detection poses a significant risk to human health and to provide a human health reference level for prometon to use for screening detections.

Table 1. Summary of the highest reported detections of prometon from the Well Inventory Database.

Chemical	DPR Chemical Code	CAS Number	Sampling Agency	Maximum Concentration Detected in a Domestic Well (ppb)	Year
Prometon	499	1610-18-0	DPR	5.9*	1986

*The highest concentration detected between 2000 and 2021 was 0.151 ppb.

cc: Carissa Ganapathy, Senior Environmental Scientist (Supervisory)