



Julie Henderson
Director

MEMORANDUM

TO: Minh Pham
Environmental Program Manager II
Environmental Monitoring Branch

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

FROM: Chunbo Zhang, PhD, Staff Toxicologist
Pete Lohstroh, PhD, Senior Toxicologist
Toxicology and Dose Response Assessment Section

Svetlana Koshlukova, PhD, Senior Toxicologist
Risk Assessment Section

DATE: June 13, 2024

SUBJECT: HUMAN HEALTH REFERENCE LEVELS FOR PYRACLONIL IN SURFACE
WATER

The Human Health Assessment (HHA) Branch at the Department of Pesticide Regulation's (DPR) was requested by the Environmental Monitoring Branch (EMB) to provide Human Health Reference Levels (HHRLs) of pyraclonil for evaluations of detected or model-estimated concentrations of its residues in surface water. This memorandum updates HHRLs of pyraclonil in surface water that reflects HHA's revised approach by establishing separate HHRLs for surface water and groundwater. The updated DPR Acute Surface Water HHRL for pyraclonil in this memorandum supersedes the corresponding HHRLs established in 2021 and 2023 (DPR, 2021c; DPR, 2023).

Conclusions and Recommendations:

1. HHA calculated Human Health Reference Levels (HHRLs) to be used for detected or model-estimated residue levels of pyraclonil 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. Based on the mode of action, pyraclonil and its degradates (M-1 (N-methyl) and M-11 (N-allyl)) are considered to have equivalent toxicity and should be summed when they are detected in the same samples.
3. Maximum residue levels of pyraclonil in surface water sources equal to or less than the DPR Acute Surface Water HHRL of 7895 parts per billion (ppb) are not expected to pose an acute risk to human health, including for sensitive subpopulations. This DPR Acute Surface Water HHRL supersedes the corresponding HHRLs (1234 and 2400 ppb) issued in 2021 and 2023, respectively (DPR, 2021c; DPR, 2023).
4. Average residue levels of pyraclonil equal to or less than the DPR Chronic Surface Water HHRL of 480 ppb in surface water are not expected to pose a chronic risk to human health, including for sensitive subpopulations.

Background

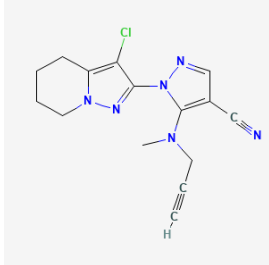
Technical Name: Pyraclonil

Chemical Name: 1-(3-chloro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyridin-2-yl)-5-[methyl(prop-2-ynyl)amino]pyrazole-4-carbonitrile

Chemical Abstracts Service Registry Number (CAS #): 158353-15-2

Molecular Weight: 314.77 g/mol (NIH, 2024a)

Chemical Structure:



(NIH, 2024a)

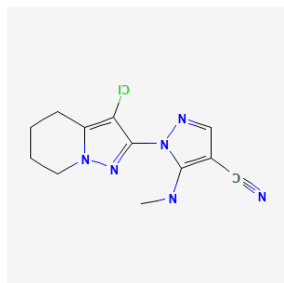
Technical Name: M-1 (N-methyl)

Chemical Name: 1-(3-Chloro-4,5,6,7-tetrahydropyrazolo[1,5- α] pyridin-2-yl)-5-(methylamino)-1H-pyrazole-4-carbonitrile

Chemical Abstracts Service Registry Number (CAS #): 158352-02-4

Molecular Weight: 276.72 g/mol (US EPA, 2023k)

Chemical Structure:



(NIH, 2024b)

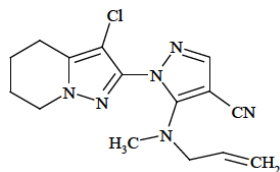
Technical Name: M-11 (N-allyl)

Chemical Name: 1-(3-Chloro-4,5,6,7-tetrahydropyrazolo[1,5- α]pyridin-2-yl)-5-(methyl(prop-2-enyl) amino)-1H-pyrazole-4-carbonitrile

Chemical Abstracts Service Registry Number (CAS #): NA

Molecular Weight: 316.79 g/mol (US EPA, 2021c)

Chemical Structure:



(US EPA, 2021c)

Pyraclonil is a light-dependent peroxidizing herbicide for multiple sedge species and broadleaf weeds in water-seeded rice. The end-use pyraclonil products are granular formulations intended to provide pre-emergence and early post-emergence controls and can be applied aerially to flooded fields or directly to soil (US EPA, 2021c; US EPA, 2023j; US EPA, 2023c). The mode of action is inhibition of protoporphyrinogen oxidase (PPO) which blocks photosynthesis and electron transfer and transport that leads to cell disruption and ultimately plant death (US EPA, 2023j). On August 17, 2023, US EPA registered pyraclonil for controlling weeds on water-seeded rice (US EPA, 2023b; US EPA, 2023g). The following month (September 2023), the first pyraclonil product was registered in California (DPR, 2024d). As of June 2024, there are two products actively registered for use in California (DPR, 2024d).

In addition to the parent chemical, it was determined that pyraclonil metabolites/degradates M-1 (N-methyl) and M-11 (N-allyl) are the residues of major concern in water (US EPA, 2023j). Residues of pyraclonil, M-1, and M-11 have similar toxicity and thus these residues may be summed if they are detected in the same samples (US EPA, 2023k).

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
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
USGS	2018	Health-Based Screening Levels for Evaluating Water-Quality Data	USGS, 2018
DPR	2020	Summary of Toxicology Data Pyraclonil	DPR, 2020
US EPA	2020	EPA Registration Division Company Notice of Filing for Pesticide Petitions Published in the Federal Register	US EPA, 2020a
US EPA	2020	Pesticide Product Registration; Applications: New Active Ingredients	US EPA, 2020b
DPR	2021	2021 Annual Statewide Pesticide Use Report Chemical Totals.	DPR, 2021a
DPR	2021	Evaluating Risk from Exposure to Illegal Pesticides on Fresh Agricultural Commodities	DPR, 2021b
DPR	2021	Evaluation Report - Pesticide: Pyraclonil	DPR, 2021c
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	2021	Pyraclonil: New Chemical Drinking Water Exposure Assessment for Use on Rice in California	US EPA, 2021c
US EPA	2021	Pyraclonil: Report of the Cancer Assessment Review Committee	US EPA, 2021d
US EPA	2022	Review of Submitted Data Relating to Claims of Greater-than-Additive (GTA) Mixture Toxicity Associated with the Proposed New Active Ingredient, Pyraclonil	US EPA, 2022
DPR	2023	Evaluation Report - Pesticide: Pyraclonil	DPR, 2023

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
OEHHA	2023	The Proposition 65 List.	OEHHA, 2023
US EPA	2023	Draft Ecological Risk Assessment and Draft Effects Determination for the New Active Ingredient Pyraclonil for use on Rice in California	US EPA, 2023a
US EPA	2023	EPA Registers New Active Ingredient Pyraclonil Released on August 24, 2023	US EPA, 2023b
US EPA	2023	Final Ecological Risk Assessment for the New Active Ingredient Pyraclonil for Use on Rice in California and its Biological Evaluation and Associated Effects Determinations for Endangered and Threatened Species and Their Designated Critical Habitats	US EPA, 2023c
US EPA	2023	Memorandum Supporting Final Decision to Approve Registration for the New Active Ingredient, Pyraclonil	US EPA, 2023d
US EPA	2023	Memorandum Supporting Proposed Decision to Approve Registration for the New Active Ingredient, Pyraclonil	US EPA, 2023e
US EPA	2023	Notice of Pesticide Registration for Pyraclonil Technical - EPA Reg # 71711-64-20230817	US EPA, 2023f
US EPA	2023	Pesticide Tolerance; Exemptions, Petitions, Revocations, etc.: Pyraclonil	US EPA, 2023g
US EPA	2023	Provisional Peer-Reviewed Toxicity Values (PPRTVs) Assessments	US EPA, 2023h
US EPA	2023	Pyraclonil. Acute, Chronic and Cancer Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for Registration of the New Active Ingredient Pyraclonil for Use on Rice	US EPA, 2023i
US EPA	2023	Pyraclonil. Human Health Risk Assessment for the New Active Ingredient for use on Rice	US EPA, 2023j
US EPA	2023	Pyraclonil. New Active Ingredient for use on Rice. Summary of Analytical Chemistry and Residue Data	US EPA, 2023k
US EPA	2023	Pyraclonil. Occupational Exposure Assessment for the Proposed Use on Water-seeded Rice for the New Active Ingredient Pyraclonil	US EPA, 2023l
US EPA	2023	Response to Public Comments on EPA's Registration of the New Active Ingredient, Pyraclonil (Docket ID: EPA-HQ-OPP-2020-0004)	US EPA, 2023m
US EPA	2023	Review of Benefits for the Proposed New Registration of Pyraclonil in Water-seeded Rice in California (DP:455657, Decision:557257)	US EPA, 2023n

Table 1. Review of Regulatory Documents and Databases

Regulatory Agency	Year	Title	Reference(s)
US EPA	2023	Status of Endocrine Disruptor Screening Program (EDSP) List 1 Screening Conclusions	US EPA, 2023o
DPR	2024	California Code of Regulations Title 3. Food and Agriculture Division 6. Pesticides and Pest Control Operations	DPR, 2024a
DPR	2024	California Pesticide Illness Query CalPIQ	DPR, 2024b
DPR	2024	Environmental Monitoring Programs and Projects	DPR, 2024c
DPR	2024	Search for Chemical Ingredient by Partial Name, Chemical Code or CAS Number	DPR, 2024d
OEHHA	2024	Public Health Goals (PHGs)	OEHHA, 2024
US EPA	2024	CompTox Chemicals Dashboard: Pyraclonil	US EPA, 2024a
US EPA	2024	Endocrine Disruptor Screening Program (EDSP) Estrogen Receptor Bioactivity	US EPA, 2024b
US EPA	2024	Human Health Water Quality Criteria and Methods for Toxicics	US EPA, 2024c
US EPA	2024	Incident Data System (IDS) - All Aggregate Summary Incidents: Methoxyfenozide	US EPA, 2024d
US EPA	2024	Integrated Risk Information System (IRIS) Glossary.	US EPA, 2024e
DPR: Department of Pesticide Regulation; US EPA: United States Environmental Protection Agency; USGS: United States Geological Survey; OEHHA: Office of Environmental Health Hazard Assessment			

Summary of Toxicology

Pyraclonil has an acute Toxicity Category¹ value of III for oral and dermal hazards and was determined to be Toxicity Category IV for inhalation hazards based on median lethal doses. It is not a skin sensitizer or an eye or skin irritant (US EPA, 2023j). US EPA classified pyraclonil as "Likely Carcinogenic to Humans" based on liver tumors observed in female mice and thyroid tumors in male rats (US EPA, 2021d; US EPA, 2023j). The cancer slope factor (CSF) or unit risk (Q1*) for pyraclonil is $1.08 \times 10^{-2} \text{ mg/kg/day}^{-1}$ in human equivalents derived from female mouse liver tumor rates (US EPA, 2023j; US EPA, 2023i). In 2023, US EPA conducted a cancer assessment for exposure to pyraclonil residues on rice and in drinking water. This assessment

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).

was based on conservative assumptions that an individual would consume rice containing the maximum allowed limit (tolerance) of pesticide residues on a chronic basis and that 100% of the crop was treated. For drinking water, the residue level was set at the maximum estimated drinking water concentration in surface water and groundwater using the Pesticide in Water Calculator (PWC) model. Based on these assumptions, US EPA concluded that the estimated exposure level had a negligible cancer risk (10^{-6} or 1 in 1,000,000) for adults 20–49 years of age (the most highly exposed adult subpopulation) and also concluded that real-world exposures and their corresponding risks would be much lower (US EPA, 2023i).

Pyraclonil 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).

In an acute neurotoxicity study, decreased motor activity and abnormal neurological responses were observed in rats 2 hours after a single dose (US EPA, 2023j). Pyraclonil targets the liver and the thyroid. Increased liver weights, increased fat deposits in liver and altered blood chemistry in mice, and increased incidences of thyroid follicular cell hypertrophy in rats were observed in subchronic studies. In chronic studies, increased incidence of hepatocellular adenomas (in mice) and thyroid follicular cell adenomas (in rats) were observed (US EPA, 2023j). Decreases in body weights were commonly seen in subchronic and chronic studies in mice, rats, and dogs (US EPA, 2023j).

HHA evaluated all required toxicity data submitted for pyraclonil registration in California (DPR, 2020) and reviewed updated US EPA regulatory documents for pyraclonil (see Table 1). For this evaluation, HHA considered toxicological endpoints and points of departure (PODs²) established by US EPA (US EPA, 2023j). The acute POD was a no observed adverse effect level (NOAEL) of 150 mg/kg/day based on decreased total motor activity counts and clinical neurotoxicity effects observed at the lowest observed adverse effect level (LOAEL) of 400 mg/kg/day in an acute neurotoxicity study in rats (US EPA, 2023j; US EPA, 2023i). This NOAEL was divided by a total uncertainty factor (UF_{TOTAL}) of 100 to calculate an acute reference dose (aRfD³) of 1.50 mg/kg/day. The UF_{TOTAL} included a 10x for interspecies extrapolation (UF_A) and 10x for intraspecies variation (UF_H) (US EPA, 2023j). HHA also uses

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> (US EPA, 2024e).

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> (US EPA, 2024e).

this aRfD of pyraclonil 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 7.3 mg/kg/day based on increased incidence of thyroid follicular cells hypertrophy in parental and F1 generations observed at LOAEL of 74 mg/kg/day in a reproductive toxicity study in rats (US EPA, 2023j). The chronic RfD (cRfD) of 0.24 mg/kg/day was calculated from dividing the NOAEL by the UF_{TOTAL} of 30 (3x for interspecies and 10x for intraspecies extrapolation) (US EPA, 2023j).

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 pyraclonil 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).

Formulae Used to Calculate Acute and Chronic Surface Water HHRLs

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

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

DWI, drinking water intake, is 95th percentile (acute) or mean (chronic) water consumption rates for non-nursing infants as described above. When a residue level of 1 parts per million (ppm) consumption defaults to the consumption rates by dimensional analysis, the acute DWI for non-nursing infants were 0.194566 (L water/kg body weight) and the chronic DWI 0.099559 (L

water/kg body weight) (US EPA, 2014). The values were rounded to two decimal points for the calculation of HHRLs (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 residue 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, 2024c).

DPR Acute Surface Water HHRL for Pyraclonil

DPR Acute Surface Water HHRLs are intended for screening maximum pesticide residue levels in surface water sources. As shown in Table 2, the DPR Acute Surface Water HHRL for pyraclonil was **7895 ppb**. Maximum residue concentrations equal to or less than the DPR Acute Surface Water HHRL of 7895 ppb are not expected to pose an acute risk to human health, including for sensitive subpopulations. This DPR Acute Surface Water HHRL supersedes the corresponding HHRLs (1234 and 2400 ppb) issued in 2021 and 2023, respectively (DPR, 2021c; DPR, 2023).

DPR Chronic Surface Water HHRL for Pyraclonil

DPR Chronic Surface Water HHRLs are intended for screening average pesticide residue levels in surface water sources. HHA calculated a DPR Chronic Surface Water HHRL of **480 ppb** for screening average pyraclonil residue levels in a surface water body (Table 2). Average residue levels of pyraclonil equal to or less than the DPR Chronic Surface Water HHRL of 480 ppb are not expected to pose a chronic risk to human health, including for sensitive subpopulations. HHA did not calculate a specific HHRL for cancer protection because US EPA's dietary (food and drinking water) assessment concluded that the cancer risk to be negligible in the highest exposed subpopulation (US EPA, 2023i).

Other Reference or Regulatory Levels for Pyraclonil 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 (MCLs⁴), non-legally enforceable Health Advisories (HAs⁵), and Human Health Benchmark for Pesticides (HHBPs⁶), and United States Geological Survey (USGS) Health-Based Screening Levels (HBSLs⁷). Federal reference or regulatory levels for pyraclonil in drinking water have not been established.

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> (US EPA, 2018a).

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> (US EPA, 2018a).

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> (US EPA, 2021b).

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/> (USGS, 2018).

Table 2. DPR Acute and Chronic Surface Water HHRLs^a for Pyraclonil and its Degradates^b

Acute or Chronic	Water Consumption Rates (L water/kg BW)	RfD (mg/kg/day)	HHRL (ppb)
Acute (maximum residues)	0.19	1.50	7895^c
Chronic (average residues)	0.10	0.24	480

BW: body weight; DPR: Department of Pesticide Regulation; 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 Pyraclonil's degradates of concern M-1 (N-methyl) and M-11 (N-allyl) are considered pyraclonil equivalents. M-1 (N-methyl): 1-(3-Chloro-4,5,6,7-tetrahydropyrazolo[1,5- α] pyridin-2-yl)-5-(methylamino)-1H-pyrazole-4-carbonitrile; M-11 (N-allyl): 1-(3-Chloro-4,5,6,7-tetrahydropyrazolo[1 5- α]pyridin-2-yl)-5-(methyl(prop-2-enyl) amino)-1H-pyrazole-4-carbonitrile.

^c The DPR Acute Surface Water HHRL for pyraclonil (7895 ppb) supersedes the corresponding HHRLs (1234 and 2400 ppb) issued in 2021 and 2023, respectively (DPR, 2021c; DPR, 2023).

The recommended HHRLs for screening pyraclonil residues in surface water are **bolded**.

Conclusions

HHA established Human Health Reference Levels (HHRLs) to be used for residue levels of pyraclonil in surface water. Pyraclonil and its degradates (M-1 and M-11) are considered to have equivalent toxicity and should be summed when they are detected in the same samples. Maximum residue concentrations of pyraclonil equal to or less than the DPR Acute Surface Water HHRL of 7895 ppb in surface water, or average residue levels equal to or less than the DPR Chronic Surface Water HHRL of 480 ppb, are not expected to pose a risk to human health, including for sensitive subpopulations. The DPR Acute Surface Water HHRL of 7895 ppb supersedes the corresponding HHRLs (1234 and 2400 ppb) issued in 2021 and 2023, respectively (DPR, 2021c; DPR, 2023).

Chunbo Zhang

Chunbo Zhang, PhD
Staff Toxicologist, Toxicology and Dose Response Assessment Section

Peter Lohstroh

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

Svetlana Koshlukova

Svetlana Koshlukova, PhD
Senior Toxicologist, Risk Assessment Section

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