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Environmental Fate of Ketamine in Soil and Relevant Waters

Roberta Xega
Bruce E. King
Kenneth B. Sumpter

RESEARCH AND TECHNOLOGY DIRECTORATE

Morgan Minyard

DEFENSE THREAT REDUCTION AGENCY
Fort Belvoir, VA 22060-6201

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14. ABSTRACT:
In this study, our objective was to assess the stability and persistence of ketamine in four soil types and seven different water sources. We wanted to determine the distribution of ketamine when it is in contact with soil and water. Soil samples in contact with waters from a variety of sources were spiked with a known amount of ketamine solution and were then extracted after several contact time points to track compound recovery and distribution. The water samples were also spiked with known amounts of ketamine, and aliquots were taken at different time points for analysis. The results showed that the amount of ketamine in contact with the soils was nearly constant for up to 12 weeks and accounted for 60–80% of the amount of the spike. Ketamine was also present in the aqueous phase, which enabled calculation of the soil-partitioning distribution coefficient, K_d. The water samples were stable up to 13 weeks. These results indicate that ketamine is relatively stable in water and moist soils. The resulting data also indicate that ketamine is mobile in the environment.

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Ketamine	Soil	Water	Opioids
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PREFACE

The work described in this report was authorized by the Defense Threat Reduction Agency (DTRA) Joint Science and Technology Office (JSTO; Fort Belvoir, VA) under project number HDTRA1620640. The work was started in November 2018 and completed in February 2019. At the time this work was performed, the U.S. Army Combat Capabilities Development Command Chemical Biological Center (CCDC CBC; Aberdeen Proving Ground, MD) was known as the U.S. Army Edgewood Chemical Biological Center.

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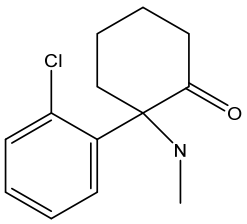
ENVIRONMENTAL FATE OF KETAMINE IN SOIL AND RELEVANT WATERS

1. INTRODUCTION

Ketamine hydrochloride (Chemical Abstracts Service number 6740-88-1; henceforth referred to as ketamine in this study) is used as an anesthetic for human and veterinary applications because of its efficacy and high safety factor. A recent comprehensive review discussed details of the applications, chemistry, pharmacology, toxicology, use, abuse, and production of ketamine.[1] The review contains recommendations concerning the appropriate measures for mitigating illicit ketamine manufacture and use. Ketamine is subject to public health concerns because of its toxic effects, which result from high dose intake, and the potential of dependency and suspected ill effects from chronic use. The ketamine structure is provided in Figure 1.



Ketamine
2-(2-chlorophenyl)-2-(methylamino)cyclohexanone
CAS No. 6740-88-1
MW = 237.73

Figure 1. Structure, formula, and molecular weight (MW) of ketamine.

In this study, our primary objective was to elucidate chemical and physical interactions between ketamine, soil, and water to advance understanding of ketamine behavior in the environment. Pesticides have been studied more extensively in the soil environment than in any other chemical class.[2] Understanding the adsorption of pesticides in soils is typically important for regulating pesticide use for crops; however, the intention of the chemical warfare defense community is to inform the warfighter about materials of concern and how they interact with the environment. For example, if a chemical is soluble in water and does not adsorb to soil, it could migrate through the soil and leach, thus contaminating ground water. Pesticides with a high-soil-partitioning distribution coefficient, K_d, adsorb strongly to soil. This relationship is typically related to the organic content of the soil and can be calculated from the pesticide soil organic partition coefficient, K_{oc}.[3] Other studies have concluded that adsorption of pesticides increases with pH and organic-matter content but decreases with ionic strength.[4]

The partitioning behavior of a pesticide or agent determines the medium in which it will concentrate: air, water, or soil. These partitioning coefficients are used by predictive models to better understand the behavior of a compound in a particular environment. The soil organic matter partitioning coefficient, K_{om}, is of particular interest in selecting useful models for future predictive modeling (such as Pearl and GeoPearl software developed in collaboration by WENR, PBL, and RIVM in the Netherlands).* This value can be calculated from the octanol-water partition coefficient, K_{ow}, which is easier to measure. Depending on the agent, additional variations in the partitioning coefficient or determining additional coefficients may be necessary. These include a pH-dependent K_{om} and the Freundlich coefficient.[5] The Freundlich coefficient is necessary when sorption of the agent is dependent on soil components other than organic matter, such as clay or other soil colloids. Determining the Freundlich coefficient is time-consuming, so a screening coefficient can be measured in advance to determine whether the Freundlich coefficient must be included in the parameter list of the agent. The screening coefficient is the same as the soil distribution coefficient, K_d, which is calculated by measuring the water and soil phase concentrations of the agent in the presence of different soils. The soils vary in pH, clay content, and organic-carbon content. A higher K_d value indicates that an agent is tightly adsorbed to soil and less likely to leach to groundwater. The K_d value can also be used to determine the organic carbon distribution coefficient constant, K_{oc}, by using the relationship $K_d = K_{oc} \times f_{oc}$, where f_{oc} is the fraction of organic carbon.[6]

In this study, we observed the stability and extractability of ketamine in four different soils for 12 weeks and seven different water sources (from various continental U.S. sites) up to 13 weeks.

2. SOIL ANALYSIS

2.1 Reagents and Chemicals

All commercial materials were used, as received. The following reagents and chemicals were used during testing:

- high-performance liquid chromatography (HPLC) grade with ≥99.9% purity acetonitrile and methanol (Sigma-Aldrich Corporation; St Louis, MO);
- in-house 16 MΩ of water (used to prepare samples and the HPLC mobile phase);
- American Chemical Society (ACS) grade with ≥99% purity sodium sulfate, sodium chloride, trisodium citrate dehydrate, and disodium hydrogen citrate sesquihydrate (Sigma-Aldrich);
- ≥99% purity calcium chloride (ACROS Organics; Pittsburg, PA); and
- ≥99% purity ketamine (Sigma-Aldrich).

*Pearl, Pesticide Emission Assessment at Regional and Local; WENR, World Education, News, and Reviews (New York, NY); PBL, Project-Based Learning; and RIVM, The National Institute for Public Health and the Environment, Netherlands.

In addition to the reagents and chemicals, 15 mL centrifuge tubes (Restek Corporation; Bellefonte, PA) with dispersive solid-phase extraction (dSPE) clean-up for 6 mL extract (Q370) were used for quick, easy, cheap, effective, rugged, safe (QuEChERS) extract clean-up. [7]

2.2 Soil Experiments

The procedures used during this portion of the study were based on Organisation for Economic Co-operation and Development (OECD; Paris, France) guideline 106.[6] This guideline contains recommendations for determining the persistence of a chemical in soil and suggests testing different naturally occurring soils with varying pH balances, clay content, and organic matter content. The following four soil types were identified and collected for detailed testing:

- Sassafras sandy loam (SSL),
- Pennsylvania Ernest silt loam (PEL),
- North Dakota loam (NDL), and
- Utah Timpie loam (UTL).

A fifth soil (Nunn clay loam from Colorado) was used to determine K_d values after 24 h of contact with the analyte. The soils were well mixed, and triplicate subsamples were analyzed by the Pennsylvania State University Agricultural Analytical Services Laboratory (University Park, PA) for texture, pH, and organic content. The soil characteristics are presented in Table 1.

Table 1. Soil Information

Soil Name and Type	Source Location	Sand Content (%)	Silt Content (%)	Clay Content (%)	Textural Class	pH	Organic Carbon Content (%)
SSL	Maryland	53	30	17	Sandy loam	4.5	1.1
PEL	Pennsylvania	34	45	21	Loam	4.5	3.9
NDL	North Dakota	28	49	22	Loam	7.6	3.1
UTL	Utah	27	47	26	Loam	8.4	1.4
*Nunn clay loam	Colorado	45	23	32	Clay loam	7.6	1.2

*Colorado Nunn clay loam data were measured and used only for K_d calculations.

2.3 Soil Collection and Processing

The SSL and NDL soil types had been previously collected for other projects at the U.S. Army Edgewood Chemical Biological Center (Aberdeen Proving Ground, MD), which

is now known as the U.S. Army Combat Capabilities Development Command Chemical Biological Center.

The remaining two soil types (PEL and UTL) were collected by removing all leafy matter from the sampling area. We dug a hole a few inches deep and then dug outward in a circle. The soil samples were collected mostly from the A horizon (topsoil), which typically consists of ~13 mm of the topmost soil portion. If O-horizon matter was present, the nonfibrous portion of the O horizon was collected and mixed with the A-horizon matter. The samples were air-dried, crushed, and sieved using a 2 mm ASTM International (West Conshohocken, PA) standard sieve. All sieved samples were stored in plastic-capped containers at room temperature. Remaining moisture levels were measured before testing was initiated, and data were reported as dry soil mass.

The OECD guideline suggests using large quantities of soil for testing (2–50 g). Because of the hazardous nature of the compound used in our work and the need to execute experiments safely and efficiently, 2 g (the minimum amount specified in the guideline) of soil was used in each of the 96 sample vials and 32 negative controls during our experiments. No soil was used for the 32 positive-control samples. The 2 g of soil, corrected for remaining moisture content in our calculations and reported as dry weight, was reconstituted with 2 mL of 0.01 M calcium chloride solution on the day before the ketamine spike was performed. Vials of soil and solution were left overnight at room temperature to fully moisten the soils.

A set of samples of each soil type was prepared for each time point. Each set was prepared in triplicate, and each set contained a positive and negative control. Each negative-control sample contained the soil type and 0.01 M calcium chloride solution but no ketamine. The no-soil, positive-control samples were prepared in calcium chloride solution only for each sample set that maintained the same sacrificial time schedule as used for the soil samples. The solution containing 2 mL of 0.01 M calcium chloride was spiked with ketamine by adding 10 µL of a 1000 µg/mL solution so that the concentration of ketamine was 5 µg/mL for each positive control.

Tubes were prepared for sacrificially collecting and extracting the ketamine at time points of 4, 24, and 48 h and 1, 2, 4, 8, and 12 weeks. A total of 160 vials were used in this portion of the work. At the time of data measurement, the tubes selected for analysis were centrifuged to separate the soil from the supernatant, and liquid phase was collected, filtered, and analyzed for ketamine using the Waters Corporation (Milford, MA) liquid chromatography–tandem mass spectrometry (LC–MS/MS) system, which has been described in detail in an earlier report.[8]

Ketamine was extracted from the soil phase using the modified QuEChERS method.[7] The modification included the addition of tris(hydroxy-methyl)aminomethane (TRIS) buffer (pH 8.3) before extraction was performed. The buffer increased the pH of the soil and ketamine solution to 8.0, thus optimizing the release of analyte from the organic matter component of the soil to allow the solution to be extracted more efficiently. The modified QuEChERS method was selected after results from several extraction methods found in the literature and technical reports were compared.

At each time point, the soil mixtures were centrifuged, and the supernatant was filtered using a 13 mm, 0.45 µm hydrophilic polyvinylidene fluoride membrane syringe filter (PALL Life Sciences Corporation; Port Washington, NY; part number [PN] 4545). After removal of the supernatant, 9 mL of TRIS buffer at pH 8.3 was added to the soil and vortexed for 30 s. Acetonitrile (10 mL) was then added, and the samples were sonicated for 30 min. Next, 4 g of magnesium sulfate was added together with 1 g of sodium chloride, 1 g of trisodium citrate dehydrate, and 0.5 g of disodium hydrogen citrate sesquihydrate. The mixture was vortexed for 30 s and then centrifuged for 5 min at 3500 rpm in a 5804 centrifuge from Eppendorf (Hamburg, Germany). The QuEChERS kit was purchased from VWR International (Radnor, PA). It contained Q-sep QuEChERS dSPE tubes for extract cleanup (Restek Original unbuffered, European EN 15662; VWR PN 10057-974). A dSPE clean-up was carried out by adding the supernatant volume (approximately 6 mL) to a 15 mL centrifuge tube containing 1.5 g of magnesium sulfate and 0.250 g of primary–secondary amine. The solution was then vortexed for 30 s. Afterwards, centrifugation was carried out at 3500 rpm for 5 min. All data were corrected for dilution, and recovery for each sample was based on the amount of ketamine found in the extraction samples at each time point.

2.4 Sample Analysis

Analysis of ketamine samples was carried out using an Acquity ultra-HPLC (Waters) system, consisting of a vacuum degasser, autosampler, and binary pump. This system was equipped with a reversed-phase pinnacle DB intrinsically base-deactivated biphenyl column of 100 × 2.1 mm with particle size 1.9 µm (Restek Corp.; PN 9409212). The liquid chromatography (LC) column temperature was maintained at 40 ºC. Mobile phases A and B consisted principally of water and methanol. The mobile phase was prepared by adding 2 mL of 1 M ammonium formate and 2 mL of 1 M formic acid to 1 L of water (A) or methanol (B), respectively. The flow rate was maintained at a constant rate of 0.35 mL/min. The LC system was run in isocratic mode, with the water/methanol ratio at 10:90 for the duration of the run. Total run time was 5 min. The analyte injection volume was 0.5 µL.

The LC system was coupled with a Waters Quattro Premier triple-quadrupole mass spectrometer (TQMS) equipped with an electrospray-ionization (ESI) interface and Mass Lynx software (Version 4.1). The TQMS system was operated in positive-ESI mode. This analytical system is henceforth referred to as the LC–MS/MS system.

Data acquisition was performed by working in selective ion-recording mode. Capillary voltage was 2.0 kV, nitrogen was used as the spray gas, source temperature was set at 120 ºC, and the optimized setting for cone voltage was 30 V.

The LC–MS/MS analytical system was calibrated before each series of measurements using standard solutions prepared from stock solutions on the day of each analysis. Two stock solutions at 1 mg/mL concentration in methanol were prepared and compared for accuracy. An eight-point calibration curve in the range of 0.01 to 1 µg/mL was determined from dilutions prepared using one of the stock solutions. A good signal-to-noise ratio was observed at the lowest calibration concentration. A calibration check sample was prepared from the second stock solution. Responses from these standards agreed to within 5%. Positive-control samples were diluted by a factor of 10 for liquid-phase analysis. Aqueous-phase samples

were not diluted because the results were below the lowest point in the calibration curve (0.01 µg/mL). Positive-control and extracted-soil samples were diluted by a factor of 4 with acetonitrile to keep the experimental concentrations in the calibration range. Ketamine solubility in water was 46 mg/mL.[9]

3. WATER ANALYSIS

We determined ketamine stability in four soil types and in seven distinct water sources, as described in this section.

3.1 Water Sources

Water samples were obtained from the following locations:

- ground water was collected on 10 July 2018 (initial pH = 5.1) from the Anita C. Leight Estuary Center (ALEC; Harford County, MD),
- 0.1 M citrate buffer (pH = 4.1) was prepared in-house,
- 1 M TRIS buffer (pH = 8.5) was prepared in-house,
- 0.2 M 3-(*N*-morpholine)propanesulfonic acid (MOPS) buffer (pH =7.2) was prepared in-house,
- sea salt 4 was prepared in-house by adding 4 g NaCl to 100 mL of deionized (DI) water (pH = 10.7; Note: this concentration was selected to simulate ocean water),
- sea salt 8 was prepared in-house by adding 8 g NaCl to 100 mL of DI water (initial pH = 10.8), and
- 0.01 M calcium chloride solution (initial pH = 7.47) was prepared in-house.

3.2 Water Sample Preparation

Samples (20 mL) of each water type were added to separate glass vials. Each vial sample, minus the negative controls for each water type, was spiked with ketamine by adding 100 µL of a 1000 µg/mL solution so that the starting concentration was 5 µg/mL for each. Samples from each water type were prepared in triplicate and a negative-control sample was prepared for each water type. The samples were stored at 22 ± 1 °C over the course of the 13 week experimental period. After each designated time period, 100 µL of solution was removed and diluted to a final volume of 1000 µL. The diluted samples were analyzed using LC–MS/MS technology after they had been stored for 4, 24, and 96 h and 1, 2, 8, and 13 weeks after preparation.

4. RESULTS AND DISCUSSION

4.1 Soil

Recovery of ketamine in soil and supernatant varied between about 60 and 75%, respectively after 12 weeks of exposure. Those data suggest long-term environmental stability of ketamine. An immediate loss of about 20% in the aqueous phase was noted for all solutions, followed by a possible slow degradation over the length of the experiment.

The data listed in Table 2 and shown graphically in Figure 2 indicate that ketamine degrades very slowly in soil. Adsorption of ketamine in the four soil types appears to be pH dependent. The soils with higher pH (i.e., UTL pH = 8.4 and NDL pH = 7.7) showed greater sorption for ketamine and lower amounts in the liquid phase than the soils with lower pH values (i.e., SSL pH = 4.5 and PEL pH = 4.5).

Table 2. Ketamine Recovery from Soil

Weeks	SSL (%)	SD (%)	UTL (%)	SD (%)	NDL (%)	SD (%)	PEL (%)	SD (%)
0.02	63	8	83	3	81	2	67	13
0.14	72	2	90	4	87	5	66	3
0.29	60	5	82	2	79	4	65	5
1.0	82	2	93	5	91	2	74	10
2.0	70	2	83	6	74	7	63	3
4.0	65	3	74	4	77	3	58	4
8.0	62	8	58	7	58	2	46	2
12.0	56	9	55	11	71	1	54	0

SD, standard deviation.

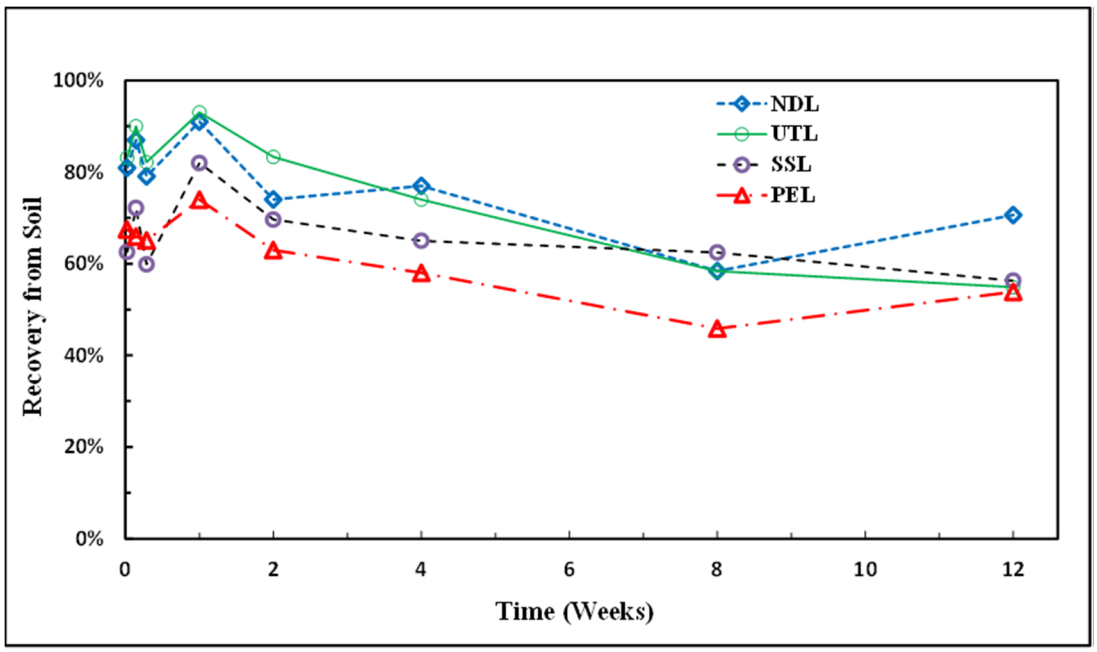


Figure 2. Ketamine recovery from soil.

Ketamine was recovered from the aqueous phase throughout the experimental period, including the samples from week 12 (Figure 3). Ketamine recovery from the supernatant was greater (10–30%) in low pH soil types, such as SSL and PEL. Less ketamine was recovered from the supernatant in higher pH soil (<10% was recovered).

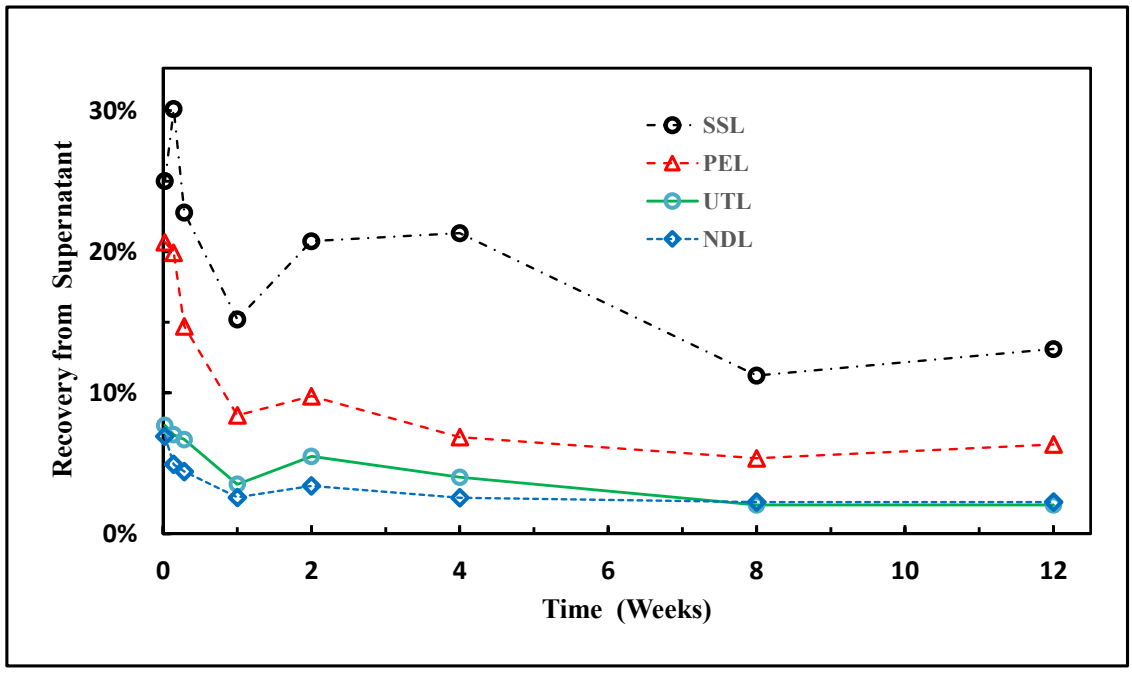


Figure 3. Ketamine recovery from supernatant.

Table 3. Ketamine Recovery from Supernatant

Weeks	SSL (%)	SD (%)	UTL (%)	SD (%)	NDL (%)	SD (%)	PEL (%)	SD (%)
0.02	25	0	8	0	7	4	21	3
0.14	30	2	7	0	5	0	20	1
0.28	23	2	7	1	4	1	15	2
1.0	15	3	4	0	3	0	8	1
2.0	21	1	5	1	3	0	10	0
4.0	21	3	4	1	3	0	7	1
8.0	11	4	2	0	2	0	5	0
12.0	13	3	2	0	2	0	6	1

K_d values are typically measured at the 24 h time point when the contaminant is expected to reach equilibrium in the soil and liquid phases. We used the extraction method described in Section 2.3, with only one difference: we added 10 mL of 0.01 M calcium chloride, as recommended by the OECD guidelines. The K_d values for all five soil types that were tested are presented in Table 3.

The K_d values were determined by using

$$K_d = \frac{C_s^{ads}(eq)}{C_{aq}^{ads}(eq)} \quad (1)$$

where

- C_s^{ads} is the content of substance adsorbed at adsorption equilibrium (μg g^{-1}) and
- C_{aq}^{ads} is the mass concentration of the substance in the aqueous phase at adsorption equilibrium (μg cm^{-3}).

The K_d values listed in Table 4 indicate a weak-to-moderate preference for ketamine to adhere to the soil as opposed to the aqueous phase. This preference is greater for the UTL and NDL soils. Both of these soil types had higher silt content than the other soil types that were tested; both were also characterized by higher pH values.

Table 4. K_d Values for Ketamine in Five Soils after 24 h

Soil Type	K_d	Clay Content (%)	pH	Organic Carbon (%)	K_{oc}
SSL	1.825	17	4.5	1.14	156
UTL	5.911	25	8.4	1.42	416
NDL	9.088	22	7.7	3.07	296
PEL	1.514	21	4.5	3.97	38
CO*	4.277	32	7.6	1.17	367

*Nunn clay loam (CO) data were used only to calculate K_d.

The organic carbon normalized adsorption coefficient K_{oc} relates the distribution coefficient K_d to the content of organic carbon of the soil sample.

Ketamine is most likely to be mobile in soil, especially in the event of runoff due to heavy rains. In particular, ketamine appeared to slowly decompose in contact with soil and water. Figure 4 shows the total ketamine recovered from soil and the supernatant for each soil.

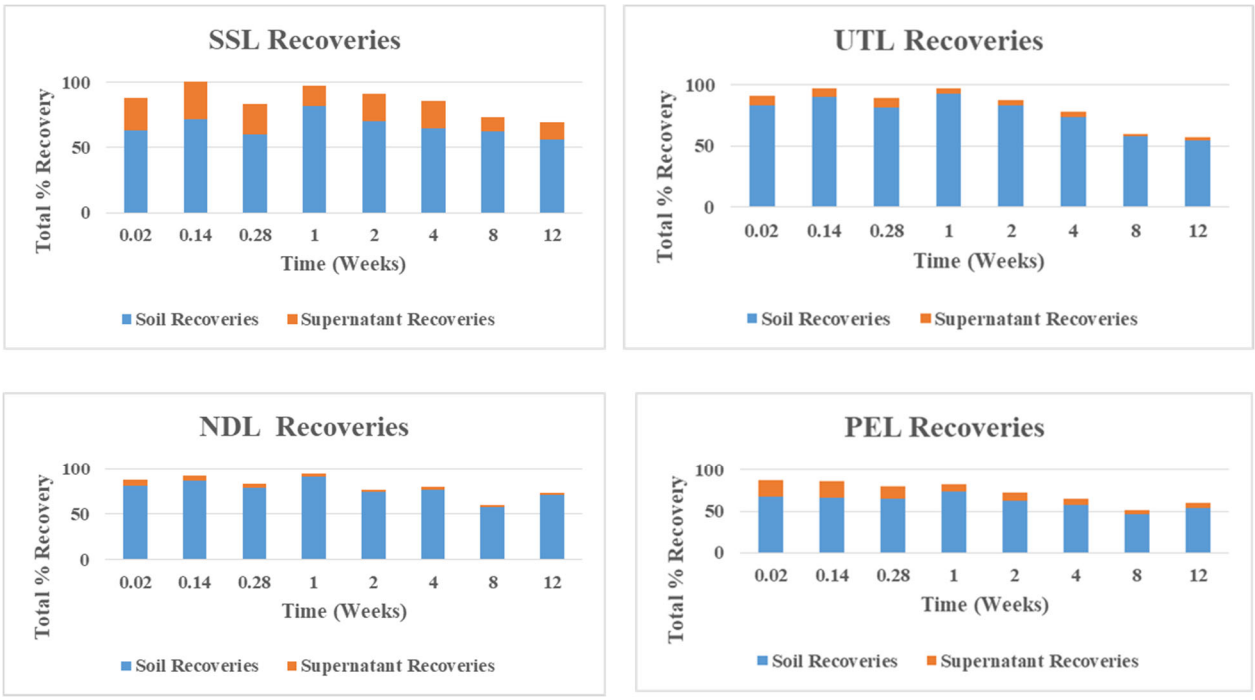


Figure 4. Ketamine total recovery.

4.2 Ketamine in Water

Ketamine stability in seven different water sources was monitored for 13 weeks. The pH values of the buffered and unbuffered samples ranged between 4 and 11 at the beginning of the trials. Water samples were not sterilized before the experiments were started because they were not collected with the intent to preserve microbial communities. No degradation was observed during the experimental period. Subsequent experiments could include microbial active samples to confirm that ketamine is not degraded by microbial activity or that it impacts the overall ecological community in the soil. Data describing recovery of ketamine from water at certain time points are presented in Table 5 and illustrated in Figure 5.

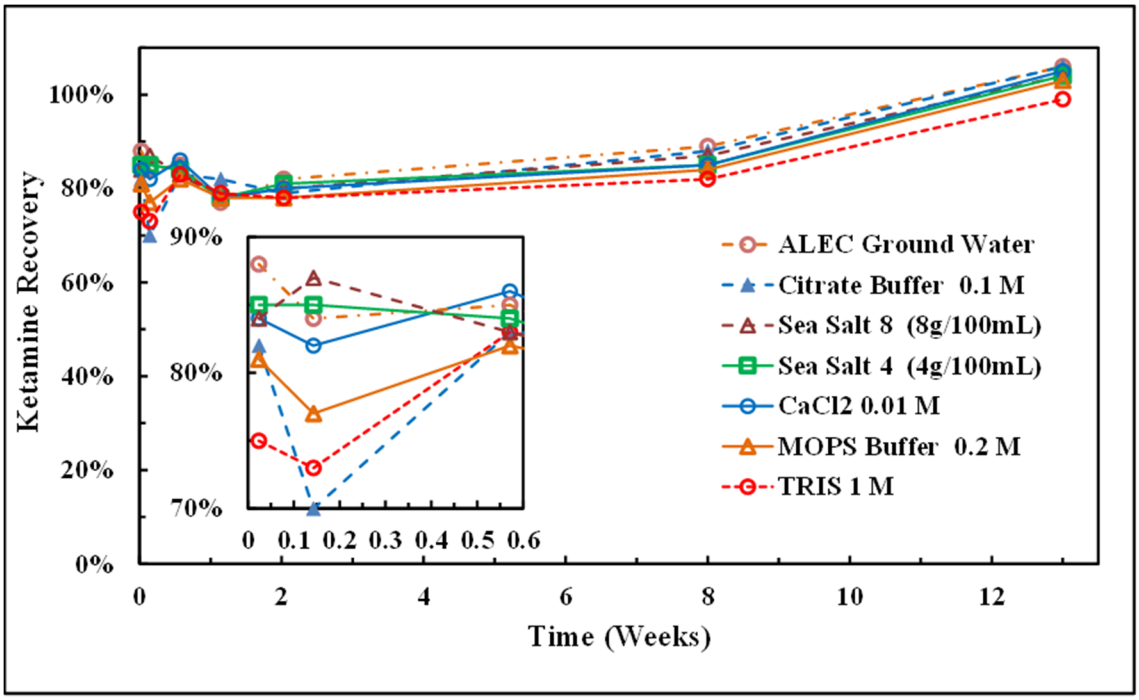


Figure 5. Ketamine recovery from seven water sources over 13 weeks.

Table 5. Ketamine Recovery from Water

Weeks	Citrate Buffer 0.1 M (%)	SD (%)	pH	TRIS 1 M (%)	SD (%)	pH	ALEC Ground Water (%)	SD (%)	pH	0.01 M $CaCl_2$ (%)	SD (%)	pH	Sea Salt 4 (%)	SD (%)	pH	Sea Salt 8 (%)	SD (%)	pH
0.02	82	2	4.12	75	2	8.51	81	1	7.24	84	1	7.47	85	1	10.68	84	1	10.81
0.14	70	0	4.08	73	3	8.55	77	5	7.26	82	3	8.00	85	9	10.51	87	2	10.69
0.57	83	1	4.08	83	0	8.50	82	1	7.26	86	2	7.76	84	1	10.45	83	1	10.45
1.14	82	1	4.04	79	1	8.55	78	1	7.33	78	1	7.57	78	0	10.26	78	0	9.97
2.03	79	2	4.09	78	1	8.39	78	2	7.19	80	2	7.24	81	2	10.00	80	1	9.73
8.00	88	3	4.14	82	1	8.50	84	2	7.23	85	2	7.10	85	2	9.51	87	1	8.54
13.00	106	1	4.00	99	1	8.31	103	1	7.23	105	4	6.96	104	4	8.87	104	0	8.23

Ketamine's persistence in water over the 13 week period was similar to its persistence in soil; ketamine did not change chemically in the environment over time. The overall behavior of ketamine agreed with our initial assumption that it is mostly found in the solid phase of soil (most likely in the organics) and persists over time. A slight concentration increase was noted in water at 13 weeks. This increase was likely due to the analytical techniques that were used and was within the experimental error.

5. CONCLUSIONS

Our study results indicate that ketamine is likely to persist in a soil environment for years. We also determined that ketamine is stable in water at ambient temperatures and a wide range of pH values for several months. In addition, the equilibrium distribution of ketamine between the soil and water types that were tested was observed to favor the soil samples. The amount of ketamine in contact with the soils was nearly constant for up to 12 weeks, accounting for 60–80% of the amount of the spike, whereas 8–25% of the spiked amount was found in the supernatant. Likewise, the water samples were shown to be stable for up to 13 weeks. These data indicate that ketamine is relatively stable in water and moist soils. The current data also suggest that ketamine is mobile in the environment, which indicates that it could percolate to ground water and other drinking sources, if not remediated, and would become stable in water over time. The amount of ketamine remaining in the soil is likely protected from degradation and could become a potential secondary hazard.

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ACRONYMS AND ABBREVIATIONS

ACS	American Chemical Society
ALEC	Anita C. Leight Estuary Center
CCDC CBC	U.S. Army Combat Capabilities Development Command Chemical Biological Center
DI	deionized
dSPE	dispersive solid-phase extraction
ESI	electrospray-ionization
f_{oc}	fraction of organic carbon
HPLC	high-performance liquid chromatography
K_d	distribution coefficient constant
K_{oc}	organic carbon distribution coefficient constant
K_{om}	organic matter partitioning coefficient
K_{ow}	octanol–water partition coefficient
LC	liquid chromatography
LC–MS/MS	liquid chromatography–tandem mass spectrometry
MOPS	3-(*N*-morpholine)propanesulfonic acid
MW	molecular weight
NDL	North Dakota loam
OECD	Organisation for Economic Co-operation and Development
PBL	Project-Based Learning
Pearl	Pesticide Emission Assessment at Regional and Local
PEL	Pennsylvania Ernest silt loam
PN	part number
QuEChERS	quick, easy, cheap, effective, rugged, safe
RIVM	The National Institute for Public Health and the Environment
SD	standard deviation
SSL	Sassafras sandy loam
TRIS	tris(hydroxy-methyl)aminomethane
TQMS	triple-quadrupole mass spectrometer
UTL	Utah Timpie loam
WENR	World Education, News, and Reviews

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