FASS

Spravato

Janssen

Nässpray, lösning 28 mg
(klar, färglös, vattenlösning)

Narkotikaklass: IV - Narkotika med medicinsk användning

Särskilt läkemedel

Psykoanaleptika, övriga antidepressiva medel

Aktiv substans:
Esketamin

ATC-kod:
N06AX27

Läkemedel från Janssen omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Esketamin

Miljörisk: Användning av esketamin har bedömts medföra försumbar risk för miljöpåverkan.
Nedbrytning: Esketamin är potentiellt persistent.
Bioackumulering: Esketamin har låg potential att bioackumuleras.

Detaljerad miljöinformation

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L)	=	$(A*10^{9}*(100-R))/(365*P*V*D*100)$ = $1.37*10^{-6}*A*(100-R)$
PEC	=	0.00068619 µg/L

Where:

A	=	total actual API sales in Sweden for the most recent year 5.0086973kg (total sold amount API in the most recent sales data for Sweden (2021) was distributed by IQVIA in 2022)
R	=	0
P	=	number of inhabitants in Sweden = $10*10^{6}$
V (L/day)	=	volume of wastewater per capita and day = 200 (ECHA default) (Reference I)
D	=	factor for dilution of wastewater by surface water flow =

10 (ECHA default)
(Reference I)

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

Algae (*Pseudokirchneriella subcapitata*) (guideline e.g. OECD 201) [Reference II]

$E\gamma C_{50}$ 72 h (yield) = 48.0 mg/L

NOECγ (yield) = 14.7 mg/L

E_rC_{50} 72 h (growth) = - (the values were greater than the highest concentration)

$NOEC_r$ (growth) = 14.7 mg/L

Crustacean (Daphnia magna) (water-flea):

Acute toxicity

EC_{50} 48 h = 106.7 mg/L (guideline e.g. OECD 202) [Reference III]

Chronic toxicity

NOEC 21 days = 3.31 mg/L (guideline e.g. OECD 211) [Reference IV]

Fish:

Acute toxicity

Oncorhynchuss mykiss (rainbow trout)

LC_{50} 96 h = 77.5 mg/L (guideline e.g. OECD 203) [Reference V]

Chronic toxicity

Danio rerio (zebrafish)

Fish early life stage test according to guideline e.g. OECD 210 [Reference VI]:

It is concluded that the NOEC of (S)-Ketamine for fry length and weight was 1.12 and

0.341 mg/L, respectively. Mortality in the 0.341 mg/L group was found to be significantly higher than that seen in the control group. There were no significant differences in mortality in any of the other test-item treated groups compared with the control.

The duration of the test was 30 days, post hatch.

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NOEC 30 days (early-life stage development - length) = 1,12 mg/L

NOEC 30 days (early-life stage development - length) = 0,341 mg/L

Other ecotoxicity data:

Activated sludge respiration inhibition test according to guideline e.g. OECD 209 [Reference VII]:

EC_{50} 3h = no value was reported because the value was estimated to be greater than 1000 mg/L

NOEC was estimated to be 100 mg/L.

PNEC (µg/l) = lowest (NOEC)/10, where 10 is the assessment factor used. NOEC for the Zebrafish (Danio rerio) of 0.341 mg/L has been used for this calculation since it is the most sensitive of the three tested species.

PNEC = 0.341 mg/L/10 = 0.0341 mg/L = 34.1 µg/L

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = 0.00068619 / 34.1 = 0.0000201229 i.e. PEC/PNEC ≤ 0.1

i.e. PEC/PNEC ≤ 0.1 which justifies the phrase “Use of S-ketamine has been considered to result in insignificant environmental risk”.

Degradation

Biotic degradation

Ready degradability:
Test results in 1.4 % degradation in 28 days according to guideline e.g. OECD 301 [Reference VIII].
Result: (S)-Ketamine was not biodegradable

Inherent degradability: -

Simulation studies:

Aerobic degradation in aquatic sediment systems:
S-ketamine was investigated for its aerobic degradation in a 100-day aquatic sediment test, according to guideline e.g. OECD 308 [Reference IX]:

Dissipation and degradation from the surface water, sediment and total system was observed following application of [14C]-S-Ketamine to sand and silt loam sediment-water systems. Kinetic modelling yielded values of 11.4 and 20.4 days,

respectively, for dissipation from the sand and silt loam surface waters. Degradation from the total system yielded DT50 values of 138 days for the sand system and 230 days for the silt loam system.

Kinetic analysis of dissipation in the sediment compartment of each system yielded DegT50 values of 252 days for the sand sediment system and 346 days for the silt loam sediment system. These are longer than the calculated DT50 values for the total system, and as the sediment is the major degradation compartment, the overall test system dissipation half-lives of 138 and 230 days may be a better indication of degradation rates in sediment. There is evidence to suggest that dissipation occurs by incorporation into sediment organic matter followed by mineralisation to CO_2.

The dissipation of S-Ketamine was fitted to single first-order (SFO) and bi-phasic model kinetics using CAKE version 3.1. The kinetic modelling results are summarized in the following table:

Charles River Sediment Code	Sediment Textural Classification	Component	DT_{50} (days)	DT_{90} (days)
S982	Sand	Surface Water	11.4	112
		Total System	138	458
S983	Silt Loam	Surface Water	20.4	127
		Total System	230	763

For all samples pooled extract was prepared by combining 70% of each of Extracts 1-4 (Extracts 1-3 where appropriate). Duplicate aliquots (1 mL) of the pooled sample were analysed by LSC and 50% of the pooled extract concentrated under nitrogen (TurboVap) until *ca* 1.0 mL of liquid remained. The concentrate was transferred

to a centrifuge tube, the concentration vessel washed/sonicated with Milli-Q water (2 mL) and the wash transferred to the centrifuge tube. This process was repeated with 2 mL of acetonitrile. The centrifuge tube containing the concentrated extract was sonicated for *ca* 5 minutes, centrifuged at *ca* 2000 rpm for *ca* 15 minutes and the supernatant transferred to a 5 mL volumetric flask. Acetonitrile (1 mL) was added to the centrifuge tube and solid residue, sonicated for *ca* 5 minutes and centrifuged at *ca* 2000 rpm for *ca* 15 minutes. The supernatant was transferred to the volumetric flask and the volume adjusted to 5 mL with Milli-Q water. Duplicate aliquots (100 µL) were analysed by LSC to confirm recovery of radioactivity.

Conclusion for degradation: S-ketamine is potentially very persistent.

Abiotic degradation

Hydrolysis: -
Photolysis: -

Bioaccumulation

Partition coefficient octanol/water:
The partition coefficient octanol/water was determined using guideline e.g. OECD 107 [Reference X].

The mean apparent log P_{OW} (distribution coefficient at a specific pH) for each n-octanol / aqueous media system was determined as follows:
Milli-RO water: Log D = -0.72 ± 0.06
pH 4 buffer: Log D = -0.72± 0.02
pH 7 buffer: Log D = 1.63 ± 0.22

pH 9 buffer: Log D = 2.06 ± 0.05

The true log P_{OW} (partition of non-ionised molecule only) was calculated from the following equation based on a dissociation constant of 7.45 for (S)-Ketamine:
Log Pow= Log D + Log(1+10(pKa-pH))
Milli-RO water: Log P_{OW} = 2.66 ± 0.41

pH 4 buffer: Log P_{OW} = 2.55 ± 0.04

pH 7 buffer: Log P_{OW} = 1.70 ± 0.24

pH 9 buffer: Log P_{OW} = 2.08 ± 0.05

Log P_{OW} values calculated from the pH 9 buffer test are expected to be most accurate since at this pH (S)-Ketamine was closest to a non-ionised state and therefore the correction calculation was most accurate.

Bioconcentration factor (BCF): -

Since log Kow < 4, S-ketamine has low potential for bioaccumulation.

Excretion (metabolism)

-

PBT/vPvB assessment

	PBT-criteria	Results for S-ketamine
Persistence	Half-life in freshwater: DT_{50} > 40 days	

	Half-life in sediment: DT_{50} > 120 days	Half-life in sediment: DT_{50} = 138days (Sand sediment)
Very Persistent	Half-life in freshwater: DT_{50} > 60 days Half-life in sediment: DT_{50} > 180 days	Half-life in sediment: DT_{50} = 230 days (Silt Loam sediment)
Bioaccumulation	BCF > 2000	No data available.
Toxicity	Chronic NOEC < 10 µg/L	$NOEC_{algae}$ = 14.7 mg/L $NOEC_{daphnia}$ = 3.31 mg/L $NOEC_{fish}$ = 0,341 mg/L

A substance is PBT if it fulfils all 3 criteria P, B, T for classification or vPvB if it fulfills 2 criteria vP, vB for classification. S-ketamine is very persistent (vP) but is not bioaccumulative or toxic. Therefore S-ketamine is not PBT (or vPvB).

References

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