FASS

Qlaira

MRx (F)

Bayer

Filmdragerad tablett

(Tabletterna är runda med bikonvexa ytor och har på ena sidan en märkning i en liksidig sexhörning. Mörkgula tabletter märkta med DD. Röda tabletter märkta med DJ. Ljusgula tabletter märkta med DH. Mörkröda tabletter märkta med DN. Vita tabletter märkta med DT.)

Gestagener och estrogener, sekvenspreparat

Aktiva substanser (i bokstavsordning):

Dienogest

Estradiol

ATC-kod:

G03AB08

Läkemedel från Bayer omfattas av Läkemedelsförsäkringen.

Miljöpåverkan

Dienogest

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

Detaljerad miljöinformation

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula:

PEC (µg/L) = $(A*10^{9}*(100-R))/(365*P*V*D*100) = 1.37*10^{-6}*A*(100-R)$ = 0.0023 µg/L

Where:

A = 16.69 kg (total sold amount API in Sweden year 2021, data from IQVIA / LIF)

R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available

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 (*green algae*, Desmodesmus subspicatus):*

NOEC 72 hours (growth rate) > 16300 µg/L, E_rC_{50} 72 hours (growth rate) > 16300 µg/L. Guideline OECD 201. (Reference II)

*Crustacean (*waterflea, *Daphnia magna):*

Acute toxicity

EC_{50} 48 hours (immobilization) > 21500 µg/L. Guideline OECD 202. (Reference III)

Chronic toxicity

NOEC 21 days (reproduction, mortality) ≥ 492 µg/L. Guideline OECD 211. (Reference IV)

*Fish (*fathead minnow, *Pimephales promelas*):

Acute toxicity

LC_{50} 96 hours (survival) ≥ 22200 µg/L. Guideline OECD 203. (Reference V)

Chronic toxicity

NOEC 21+26 d pre-exposure days (hatch and survival) = 0.064 µg/L. Guideline OECD 210 (extended). (Reference IV)

NOEC 61 days post hatch (hatch and survival) = 0.036 µg/L. Guideline OECD 210 (extended). (Reference VII)

The PNEC was calculated by division of the lowest effect level (NOEC) of the most sensitive taxonomic group considering an appropriate assessment factor (AF). The most sensitive taxonomic group were fish and the lowest effect level was reported as NOEC = 0.036 mg/L. The regulatory default standard AF of 10 was used, which is applicable when there are chronic aquatic toxicity studies representing the three trophic levels (algae, crustaceans, and fish).

PNEC = 0.036 µg/L / 10 = 0.0036 µg/L

Environmental risk classification (PEC/PNEC ratio)

The risk quotient PEC/PNEC was calculated with 0.0023 µg/L / 0.0036 µg/L = 0.64.

Justification of chosen environmental risk phrase:

A risk quotient between 0.1 and 1 qualifies for the phrase “Use of dienogest has been considered to result in low environmental risk.”.

Degradation

Biotic degradation

Ready degradability:

Dienogest was studied for aerobic biodegradability in water in a manometric respiration test according with activated municipal sewage sludge. The test item was introduced into the test system at a concentration of approximately 70 mg/L. The study reported less than 3 % biodegradation of dienogest in 28 days. Guideline OECD 301. (Reference VIII)

Simulation studies:

The transformation of dienogest in sediments and natural water was assessed in two different aerobic sediment/water systems. Dienogest was incubated in glass vessels containing sediment and overlaying water over 100 days. The results of the study indicate that dienogest is distributed to the sediment

compartment, since dienogest was removed to more than 97 % from the water phase after 100 days. The disappearance half-life DT50 in water could be determined but there was no ultimate biodegradation in sediment or the total test system.
with 5.7 and 12.3 days for the fine and coarse sediment, respectively. There was no ultimate biodegradation and the DT50 could therefore not be calculated for sediment or the total test system.
This study reported a half-life of substance dienogest in water DT_{50} = 5.7-12.3 days, while no DT_{50} could be determined in sediment/total system and is therefore considered > 120 days. Guideline OECD 308. (Reference IX)

Abiotic degradation

Hydrolysis:
Dienogest was reported to be hydrolytically stable. Guideline OECD 111. (Reference X)
Justification of chosen degradation phrase:
Dienogest established a DT_{50} > 120 d for the total system and is resistant to hydrolysis, which qualifies for the phrase “dienogest is potentially persistent.”.

Bioaccumulation

Partitioning coefficient:
The log D_{ow} was reported with 1.6 at pH 7. Guideline OECD 117. (Reference XI)
Justification of chosen bioaccumulation phrase:
As the log D_{ow} was < 4 dienogest is not considered bioaccumulative which qualifies for the phrase “dienogest has low potential for bioaccumulation.”.

Excretion (metabolism)

Systemically available dienogest is mainly excreted in the hydroxylated form, a small fraction (6-8 %) has been detected unchanged or as conjugate in urine (Reference XII, XIII)

References

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X. Dienogest/ZK 37659/Report on physicochemical properties/Rate of hydrolysis. Analytical Development Physical Chemistry, Schering AG, study no. 05600183, report no. A28384
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XII. Detection and identification of STS 557 metabolites in human (female) urine by liquid chromatography coupled to mass spectrometry. Biotec Centre, Orleans, France. ScheringAG/Biotec Centre, Orleans, France. Original Study No.: 98124, report no. B455 (1994)
XIII. Tolerability and pharmacokinetics of a single oral dose of DNG in healthy adult Japanese females. Schering AG/Mochida Japan, Original Study no. N/Ap, report no. A00681 (1997)

Estradiol

Miljörisk: Användning av estradiol har bedömts medföra medelhög risk för miljöpåverkan.
Nedbrytning: Estradiol bryts ned långsamt i miljön.
Bioackumulering: Estradiol har låg potential att bioackumuleras.

Detaljerad miljöinformation

Estradiol valerate, estradiol hemihydrate

Estradiol valerate is an ester of estradiol. Estradiol hemihydrate is estradiol containing one molecule of water per molecule estradiol. The biological active moiety of these compounds is 17ß-estradiol. Therefore, this classification is based on estradiol.

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

In order to normalize the different estradiol esters on the active ingredient estradiol, all sales volumes are adjusted to the molecular weight of estradiol. For polyestradiol phosphate the molecular weight of one unit estradiol phosphate is used.

Estradiol	272.4 g/Mol	--
Estradiol valerate	356.5 g/Mol	0.75
Estradiol hemihydrate	562.8 g/Mol	0.48

PEC is calculated according to the following formula:
PEC (µg/L) = (A*10^9*(100-R)) / (365*P*V*D*100) = 1.5*10^-6*A*(100-R)

Where:
A = 24.08 kg estradiol equivalents as the total of 19.02 kg estradiol valerat and 19.72 kg estradiol hemihydrate (total sales data in Sweden in 2019 from IQVIA database).
R = 0 % removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available.
P = number of inhabitants in Sweden = 9*10^6
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default) (1)(1)
D = factor for dilution of wastewater by surface water flow = 10 (1)

Based on this formula and data the PEC was calculated as 0.0036 µg/L = 3.6 ng/L.

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies

(All studies were performed with estradiol as active moiety in estradiol-esters such as valerate or hemihydrate)

Algae (Desmodesmus subspicatus):

EC50 72 h (growth inhibition, growth rate) = > 3100 µg/L (as estradiol) (OECD TG 201).

(2)(1)

Crustacean (waterflea Daphnia magna):

Chronic toxicity NOEC 21 days (reproduction) = ≥

139 µg/L (reproduction, mortality) (FDA TAD 4.09). (3)

Fish:

Acute toxicity (Rainbow trout Oncorhynchus mykiss)

LC50 96 h (mortality) = > 500 µg/L (guideline FDA TAD 4.11). (4)

Chronic toxicity (fathead minnow Pimephales promelas):

EC10 56 d (weight) = 0.008 µg/L (EPA FIFRA Subdev. E, 72-5). (5)

The lowest chronic NOEC or EC10 was determined with fish (*Pimephales promelas*) and used to calculate the PNEC applying an assessment factor of 10: 0.008 µg/L / 10 = 0.0008 µg/L = 0.8 ng/L.

Environmental risk classification (PEC/PNEC ratio)

The PEC/PNEC ratio calculates as 3.6 ng/L / 0.8 ng/L = 4.5, i.e. the ratio is > 10, which justifies the phrase "Use of estradiol has been considered to result in moderate environmental risk."

Degradation

Biotic degradation

Ready degradability: not readily biodegradable, but significant mineralization

Estradiol was studied for aerobic biodegradability in a study according to OECD 301 B and in two studies according to FDA TAD 3.11. In all studies, estradiol was determined to degraded to more than 60 % after 28 days, however, failing the criterion for ready biodegradation.(6)(7)(8)

Abiotic degradation

Hydrolysis: Estradiol is hydrolytically stable (9).

Due to the high mineralization rate in the ready biodegradability test, the phrase “estradiol (as valerate or hemihydrate) is slowly degrading in the environment” applies.

Bioaccumulation

Partitioning coefficient: Log KOW 4.03 (FDA TAD 3.02) (10).

In addition, a bioaccumulation study according to OECD TG 305 was conducted (11). 20 fish (Lepomis macrochirus) were exposed to14C labeled estradiol as well as 40 fish in the tap water control and exposed for an uptake period of 22 days, followed by 8 days depuration.There were 2 replicates per treatment and 1 for the control.

The test substance solution was delivered continuously to the tanks. The nominal concentration of estradiol in the water was 276 ng/L. The concentration of the test substance in the fish and in the water was determined in the uptake and depuration phase of the test.

The 14C concentration in the fish was analyzed by liquid scintillation after oxidative degradation of the fish in samples taken on day 4, 6, 10, 14, 21, 24, 26, and 30. The 14C concentration in the water was analyzed by liquid scintillation in samples taken at the same time points.

The bioconcentration factor in fish (BCFss) was calculated as the ratio of the mean values of the 14C concentration in fish and in water.
The BCFss was 108.8 (normalized to 6% lipid: 85.9). The uptake rate constant (k1) was 1.1, the depuration rate constant (k2) was -2.2. The DT50 for depuration was determined with 3.2 days, indicating a rapid turnover of estradiol. This finding could be expected, since estradiol is an endogenous hormone metabolized rapidly during normal physiological processes.

Justification of chosen bioaccumulation phrase:
The log KOW of 4.03 fulfills the screening criterion, while the BCF of 108.8 is clearly below the threshold of 500. Therefore, the phrase “The substance has a low potential for bioaccumulation” applies.

Excretion (metabolism)
Estradiol valerate are readily cleaved into estradiol and valeric acid. Estradiol undergoes the same metabolic pathways as endogenous estrogen, i.e. it is further metabolized into the major metabolites estrone, estriol, estrone sulfate and estrone glucuronide (12), (13), (14).

PBT/vPvB assessment
As the BCF of estradiol is 108.8 and clearly below the threshold of 2000 the substance is not PBT or vPvB.

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