Environmental Risk Assessment Data
Dapagliflozin

Dapagliflozin is used for the treatment of patients with type 2 diabetes and has been developed by an alliance between AstraZeneca and Bristol-Myers Squibb. It is a selective and reversible inhibitor of sodium-glucose co-transporter 2 (SGLT2). SGLT2 is a protein that absorbs glucose from the urine into the bloodstream as the blood is filtered in the kidneys. By blocking the action of SGLT2, dapagliflozin causes more glucose to be removed via the urine, thereby reducing the levels of glucose in the blood. Dapagliflozin works independently of insulin for the treatment of type 2 diabetes, as an adjunct to diet and exercise, in combination with other glucose-lowering medicinal products including insulin, and in metformin intolerant patients.

Dapagliflozin is an active pharmaceutical ingredient in the following AstraZeneca products: Forxiga, Xigduo and Qtern.

Dapagliflozin is mainly excreted as metabolites; the primary route being via the urine. Approximately 17% of the dose is excreted as unchanged parent, mainly via the faeces.

Dapagliflozin is not readily biodegraded, however, in the aquatic environment, there is evidence that the substance will be extensively degraded within aquatic sediments. Dapagliflozin is not predicted to bioaccumulate in aquatic organisms.

The Predicted Environmental Concentration (PEC) / Predicted No Effect Concentration (PNEC) ratio is $9.2 \times 10^{-5}$, which means use of Dapagliflozin is predicted to present an insignificant risk to the environment.

Predicted Environmental Concentration (PEC)
The PEC is based on the following data:

$PEC = \frac{A \times 10^9 \times (100-R)}{365 \times P \times V \times D \times 100}$

$A$ (kg/year) = total patient consumption in the European country with the highest per capita use in 2016 (Source: IMS Health$^1$)
$R$ (%) = % removal during wastewater (sewage) treatment (due to loss by adsorption to sludge particles, by volatilisation, hydrolysis or biodegradation). For Dapagliflozin, it is assumed that $R = 0$ as a worst case.
$P = $ number of inhabitants in the country with the highest per capita use (Source: IMS Health$^2$).
$A/P = 6.74 \times 10^{-6}$ kg/inhabitant
$V$ (L/day) = volume of wastewater per capita and day = 200 (European Medicines Agency (EMA) default value (Ref. 1))
$D = $ factor for dilution of waste water by surface water flow = 10 (EMA default value)
(Note: The factor $10^9$ in the equation above converts the quantity used from kg to μg)

PEC = 0.0092 μg/L

(Note: Whilst Dapagliflozin is metabolised in the body, little is known about the ecotoxicity of the metabolites. Hence, as a worst case, for this calculation, it is assumed that 100% of excreted metabolites have the same ecotoxicity as Dapagliflozin).

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$^1$ IMS Health, MIDAS International Data for 2016, available for 21 European markets
Accessed: 20/4/17
Predicted No Effect Concentration (PNEC)
Long-term tests have been undertaken for species from three trophic levels, based on internationally accepted guidelines. Therefore, the PNEC is based on the lowest NOEC value 1 mg/L (equivalent to 1,000 µg/L) which was reported for *Pimephales promelas* and an assessment factor of 10 is applied, in accordance with ECHA guidance (Ref. 2).

\[
PNEC = \frac{1,000 \ \mu g/L}{10} = 100 \ \mu g/L
\]

**PEC/PNEC**
PEC = 0.0092 µg/L  
PNEC = 100 µg/L  

\[
PEC/PNEC = 9.2 \times 10^{-5}
\]

The PEC/PNEC ratio of $9.2 \times 10^{-5}$ corresponds to the phrase ‘Use of the dapagliflozin has been considered to result in insignificant environmental risk’ in the www.fass.se scheme (Ref 3).

**Environmental Fate Summary**
Dapagliflozin is water soluble and is hydrolytically stable in the aquatic environment. It cannot be classified as readily biodegradable and in domestic sewage treatment, it is unlikely to significantly partition to the sludge solids. In the water-sediment transformation study (OECD308) dapagliflozin rapidly dissipated from the water phase into the aquatic sediments, the half-life from water was 6 - 8.7 days. In the sediment phase, there was evidence of extensive degradation with the formation of multiple transformation products and the extensive formation of $^{14}$CO$_2$; the half-life from sediment was 95 - 128 days. Overall this study shows that dapagliflozin is unlikely to persist in the aquatic environment.

Dapagliflozin is not ionisable within the environmentally relevant pH range (estimated pKa = 12.6). The octanol-water partition coefficient, measured at environmentally relevant pH 7.4, is low and dapagliflozin is not predicted to bioaccumulate in aquatic organisms.

**Aquatic Toxicity Data for Dapagliflozin**

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Method</th>
<th>Result</th>
<th>Ref</th>
</tr>
</thead>
</table>
| Activated sludge, respiration inhibition test | OECD209 | 3 h EC50 >200 mg/L  
3 h NOEC = 200 mg/L | 4 |
| Toxicity to green algae, *Pseudokirchinella subcapitata*, growth inhibition test | OECD201 | 72 hour NOEC$_{growth\ rate}$ = 37 mg/L  
72 hour LOEC$_{growth\ rate}$ = 67 mg/L  
72 hour EC50$_{growth\ rate}$ = 120 mg/L  
72 hour NOEC$_{biomass}$ = 21 mg/L  
72 hour LOEC$_{biomass}$ = 37 mg/L  
72 hour EC50$_{biomass}$ = 48 mg/L | 5 |
| Acute toxicity to *Daphnia magna* | OECD202 | 48 hour EC50 >120 mg/L  
48 hour NOEC = 120 mg/L | 6 |
| Fish early-life stage toxicity with fathead minnow, *Pimephales promelas* | OECD210 | 32 day NOEC = 1.0 mg/L  
32 day LOEC > 1.0 mg/L based on hatch, survival, standard length, and dry weight | 7 |
### Environmental Fate Data for Dapagliflozin

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<tr>
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<tbody>
<tr>
<td>Aerobic biodegradation</td>
<td>OECD301F</td>
<td>11% after 28 days. Not readily biodegradable</td>
<td>10</td>
</tr>
<tr>
<td>Adsorption/desorption to sludge</td>
<td>OPPTS guideline 835.1110</td>
<td>$K_d(ads) = 51 \text{ L/Kg}$ $K_{oc} = 138 \text{ L/Kg}$</td>
<td>11</td>
</tr>
<tr>
<td>Aerobic transformation in aquatic sediment systems</td>
<td>OECD308</td>
<td>• Mass balance 83-120% of applied radioactivity</td>
<td>12</td>
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<tr>
<td></td>
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<td>• The half-lives (DT50) in the water 6.0 – 8.7 days</td>
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<tr>
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<td>• The half-lives (DT50) in the sediment ranged 95 - 128 days</td>
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<td>• Extensive mineralisation ($^{14}$CO$_2$ formation) observed in both high and low organic matter vessels with 45 and 76% of the applied radioactivity after 148 days</td>
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<td>• $K_{sediment} = 12 \text{ kg/L}$, based on measured partitioning at 8 days</td>
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</table>

**Kd** Distribution coefficient for adsorption  
**Koc** Organic carbon normalized adsorption coefficient

### Physical Chemistry Data for Dapagliflozin

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<tbody>
<tr>
<td>Octanol-water distribution coefficient</td>
<td>OECD107, Shake flask</td>
<td>$\log P_{ow} = 2.34$ at pH 7</td>
<td>13</td>
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</tbody>
</table>
| Water solubility              | OECD105, Shake flask    | pH 5 = 720 mg/L
pH 7 = 538 mg/L
pH 9 = 946 mg/L                                                         | 14  |
| Hydrolysis                    | OECD111                 | <10% after 5 days at 50°C (pH 5 and 7)  
11.5% after 5 days at 50°C (pH 9)  
t½ at 25°C ≥ 1 year                                                       | 15  |
References


