Environmental Risk Assessment Summary
Carvedilol

Introduction

The publication of environmental risk assessment summaries is part of Roche’s engagement on developing a better understanding of issues regarding pharmaceuticals in the environment (PiE).

New pharmaceutical substances are investigated for biodegradability and initial ecotoxicity during their development. For registration, a full state-of-the-art environmental risk assessment is developed based on chronic environmental effects and advanced environmental fate data, as required by the pertinent regulations. While not a regulatory requirement, Roche also investigates older pharmaceutical substances, normally at a simpler scale, in order to assess their environmental risks.

For active pharmaceutical ingredients, the potential environmental risk is calculated from the ratio between the predicted environmental concentration (PEC) of the substance in the aquatic environment based on a conservative emission scenario and the predicted no effect concentration (PNEC), a concentration below which no adverse effects on the environment have to be expected.

Summary

Carvedilol, a beta-blocker, is used for the treatment of hypertension and chronic heart failure (CHF). It is the active pharmaceutical ingredient used in the Roche product Dilatrend [9].

Carvedilol is extensively metabolized in the liver, glucuronidation being one of the main reactions. The demethylation and hydroxylation at the phenol ring produce 3 active metabolites with blocking activity of beta-adrenergic receptors [5].

The average half-life of elimination of carvedilol is approximately 6 hours. The plasma clearance is approximately 500–700 ml/min. Elimination is mainly via the bile, and excretion mainly via the faeces. A minor part is eliminated renally in the form of various metabolites [5].

Carvedilol is not readily biodegradable. However, the calculated biodegradation based on DOC measurements reached 94 %. This elimination is presumably only due to adsorption to the activated sludge and not due to biodegradation [4].

The PEC/PNEC ratio is 0.13. With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [7], a PEC/PNEC ratio of ≤1 means that Carvedilol and/or its metabolites are unlikely to represent a risk to the aquatic environment.
**Predicted Environmental Concentration (PEC)**

The PEC is based on the following data:

\[
\text{PEC (µg/L)} = \frac{(A \times 10^9 \times (1-R))}{(365 \times P \times V \times D)}
\]

- **A** Total patient consumption of Carvedilol in the European country with the highest yearly per capita use in the period 2013–2017 (data from IQVIA [11])
- **R** Removal rate during sewage treatment = 0.55 (55% as calculated by the fate and emission prediction model SimpleTreat 4.0 [12])
- **P** Number of inhabitants in the country with the highest per capita use in the respective year of the period 2013–2017 [8]; resulting in a consumption of 60.5 mg/inhabitant
- **V** Volume of wastewater per inhabitant and day (default value) = 200 L day\(^{-1}\) [7]
- **D** Dilution factor of wastewater by surface water flow (default value) = 10 [7]

PEC = 0.0373 µg/L

*Note:* Carvedilol is at least partially metabolised in the body. Since little is known about the ecotoxicity of these metabolites, it is assumed as a worst case that they have the same ecotoxicological relevance as Carvedilol.

**Predicted No Effect Concentration (PNEC)**

The PNEC is derived from the lowest EC50/LC50 from acute studies with algae, *Daphnia* and fish by applying an assessment factor of 1000. The lowest LC50 is 0.29 mg/L of the 96 h fish acute toxicity study with rainbow trout (*Oncorhynchus mykiss*) according to OECD 203 [10]. Applying an assessment factor of 1000 according to the REACH Guidance [6] results in a PNEC value of 0.29 µg/L.

PNEC = 0.29 mg/L ÷ 1000 = 0.29 µg/L

**PEC/PNEC ratio**

PEC = 0.0373 µg/L
PNEC = 0.29 µg/L

PEC/PNEC = 0.13

With reference to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use of the European Medicines Agency [7], a PEC/PNEC ratio of 0.13 (i.e. ≤1) means that Carvedilol and/or its metabolites are unlikely to represent a risk to the aquatic environment.
**Aquatic Toxicity Data for Carvedilol**

<table>
<thead>
<tr>
<th>Study</th>
<th>Guideline</th>
<th>Results</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algal growth inhibition test with the green alga Desmodesmus subspicatus</td>
<td>OECD 201</td>
<td>72 h EC50 (growth rate) 1.48 mg/L NC&lt;br&gt;72 h EC50 (yield) 1.34 mg/L NC&lt;br&gt;72 h EC50 (growth rate) 0.82 mg/L MIC&lt;br&gt;72 h EC50 (yield) 0.72 mg/L MIC&lt;br&gt;72 h NOEC 0.23 mg/L MIC&lt;br&gt;72 h EC50 1.6 mg/L&lt;br&gt;72 h NOEC 0.46 mg/L</td>
<td>[1]</td>
</tr>
<tr>
<td>Acute immobilisation test with <em>Daphnia magna</em></td>
<td>OECD 202</td>
<td>48 h EC50 7.38 mg/L TWA&lt;br&gt;48 h NOEC 0.89 mg/L TWA&lt;br&gt;48 h EC50 1.8 mg/L&lt;br&gt;48 h NOEC 0.35 mg/L</td>
<td>[2]</td>
</tr>
<tr>
<td>Chronic reproduction test with Ceriodaphnia dubia</td>
<td>NA</td>
<td>8 d NOEC 0.25 mg/L</td>
<td>[10]</td>
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<tr>
<td>Acute toxicity to guppy (<em>Poecilia reticulata</em>)</td>
<td>OECD 203</td>
<td>96 h LC50 &gt;0.81 mg/L TWA&lt;br&gt;96 h NOEC 0.81 mg/L TWA</td>
<td>[3]</td>
</tr>
<tr>
<td>Acute toxicity to bluegill sunfish (<em>Lepomis macrochirus</em>)</td>
<td>OECD 203</td>
<td>96 h LC50 0.99 mg/L&lt;br&gt;96 h NOEC &lt;0.43 mg/L</td>
<td>[10]</td>
</tr>
<tr>
<td>Acute toxicity to rainbow trout (<em>Oncorhynchus mykiss</em>)</td>
<td>OECD 203</td>
<td>96 h LC50 0.29 mg/L&lt;br&gt;96 h NOEC 0.025 mg/L</td>
<td>[10]</td>
</tr>
<tr>
<td>Respiration inhibition test</td>
<td>OECD 209</td>
<td>3 h IC50 98 mg/L</td>
<td>[10]</td>
</tr>
<tr>
<td>Bacteria toxicity in biodegradation test (toxicity control)</td>
<td>OECD 301 F</td>
<td>14 d NOEC 100 mg/L</td>
<td>[4]</td>
</tr>
</tbody>
</table>

EC50 Concentration of the test substance that results in 50% effect<br>IC50 Concentration of the test substance that results in 50% inhibition<br>LC50 Concentration of the test substance that results in 50% mortality<br>MIC (Measured) initial concentration<br>NC Nominal concentration<br>NOEC No Observed Effect Concentration<br>TWA Time weighted average

**Environmental Fate Data for Carvedilol**

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<tr>
<td>Ready biodegradability test</td>
<td>OECD 301 F</td>
<td>0% after 28 days (BOD)&lt;br&gt;94% after 28 days (DOC)&lt;br&gt;96% after 28 days (HPLC)</td>
<td>[4]</td>
</tr>
<tr>
<td></td>
<td>OECD 301 B</td>
<td>25% after 28 days (CO2)</td>
<td>[10]</td>
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BOD Biochemical oxygen demand<br>CO2 Carbon dioxide (mineralisation)<br>DOC Dissolved organic carbon
## Physical Chemical Data for Carvedilol

<table>
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<th>Study</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Water solubility</td>
<td></td>
<td>14.7 mg/L (22 °C)</td>
<td>[4]</td>
</tr>
<tr>
<td><em>n</em>-Octanol/Water Partition Coefficient</td>
<td>NA</td>
<td>log P&lt;sub&gt;OW&lt;/sub&gt; = 4.19</td>
<td>[9]</td>
</tr>
<tr>
<td><em>n</em>-Octanol/Water Distribution Coefficient</td>
<td>NA</td>
<td>1.98 (pH 5)</td>
<td>[10]</td>
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<td></td>
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<td>2.73 (pH 7)</td>
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<td>3.03 (pH 9)</td>
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</table>

## References

[3] BMG Engineering Ltd, on behalf of F. Hoffmann-La Roche Ltd, Basel, Switzerland (2004): Carvedilol: 96-hour acute toxicity to *Poecilia reticulata* (Guppy), limit test. BMG study no. 765/c-03
[11] IQVIA MIDAS Quantum, Q1 2018