Critical evaluation of different inputs for the estimation of pharmaceuticals exposure seeking an improved environmental risk assessment

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Summary

- Objectives
- Introduction
- Materials and methods
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- Conclusions

Objectives

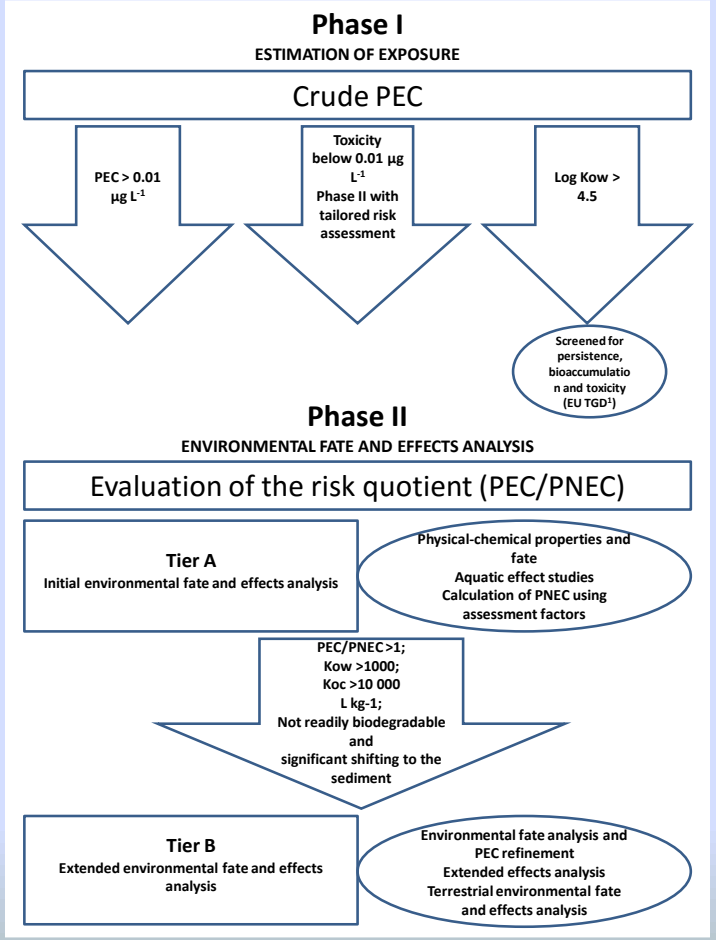
- Discuss a general tiered approach for estimating the Predicted Environmental Concentrations (PECs) based on the European Medicines Agency (EMA) Guideline
- Critically evaluate uncertainties in PEC calculations
- Assess which parameters included in the PEC estimation are more crucial
- Use PECs formula to perform risk assessment

Introduction

- In recent years, has been observed an increased consumption of pharmaceuticals across the world
- Due to their characteristics, several hundred pharmaceuticals have been found in the aquatic environment
- They are continuously introduced into the environment (chronic exposure) and can induce toxicity in aquatic organisms
- Pharmaceutical exposure assessments may be conducted by means of either monitoring programs, which result Measured Environmental Concentrations (MECs), or by means of prediction models
- However, a comparison between MECs and the PECs, considering the parameters included in the PECs calculation, is required to assess its validity

EMA guideline on risk assessment

- European Medicines Agency (EMA) issued a Guideline on ERA of Medicinal Products for Human Use in 2006
- The ERA Guideline consists of two phases
- Phase II can have two tiers
- A risk quotient higher than 1 does not prevent a new marketing authorization
- ERAs is not performed in products that made it to the market before 2006
- Despite this awareness, legal limits have not yet been set for pharmaceuticals in surface water



Materials and methods

- 16 pharmaceuticals, based on their national consumption and supported by two Portuguese extensive studies, were selected

- These studies were performed on wastewater effluents (WWE)

- PECs for surface water are derived from the PEC in WWE, considering a dilution factor of 10

- Worst case scenario approach was used

Different approaches for PECs calculation

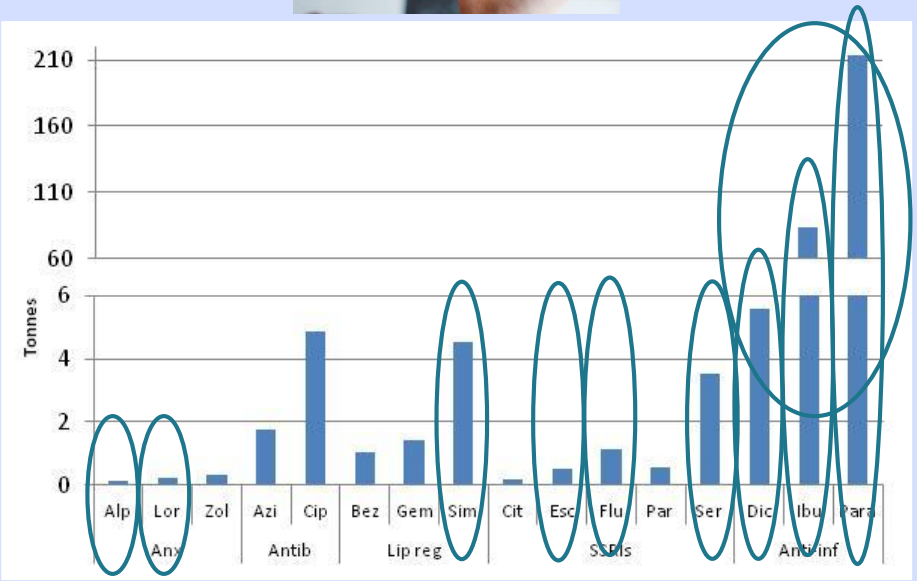
- Eq. 1 - The one advocated by EMA guideline for ERA $PEC = \frac{DOSEai * Fpen}{WASTEWinhab}$
- Eq. 2 – Adding national consumption $PEC = \frac{NatCons}{WASTEWinhab * NatPop}$
- Eq. 3 – Adding human excretion $PEC = \frac{Fexcreta * NatCons}{WASTEWinhab * NatPop}$
- Eq. 4 – Adding WWTPs removal efficiencies $PEC = \frac{Fexcreta * NatCons * WASTEWremo}{WASTEWinhab * NatPop}$
- Eq. 5 – Adding volume of wastewater produced $PEC = \frac{Fexcreta * NatCons * WASTEWremo}{PORTWASTEWinhab * NatPop}$
- The best approach was selected by inverse modelling, comparing these results with MECs in WWE

- Consumption regarded 2013 national sales
- Excretion rates, removal efficiencies and wastewater produced by the Portuguese population were collected by literature review
- MECs were obtained from 6 studies
- Risk quotients (RQs) were determined

Results and discussion

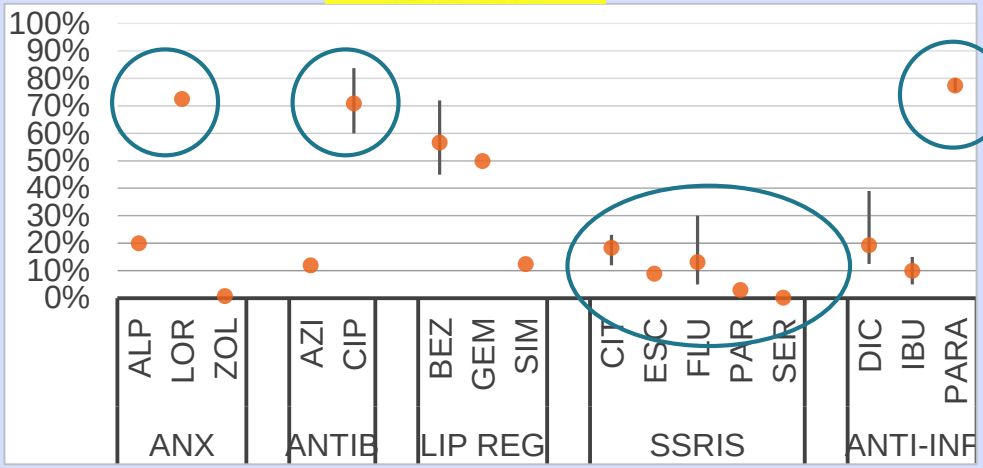
Comsumption

- 323 tonnes of the selected pharmaceuticals were dispensed in 2013
- Anti-inflammatories had markedly higher values, accounting for 303 tonnes per year
- 9 of the 16 pharmaceuticals had penetration factors over 0.01 and up to 0.0394 (SIM)



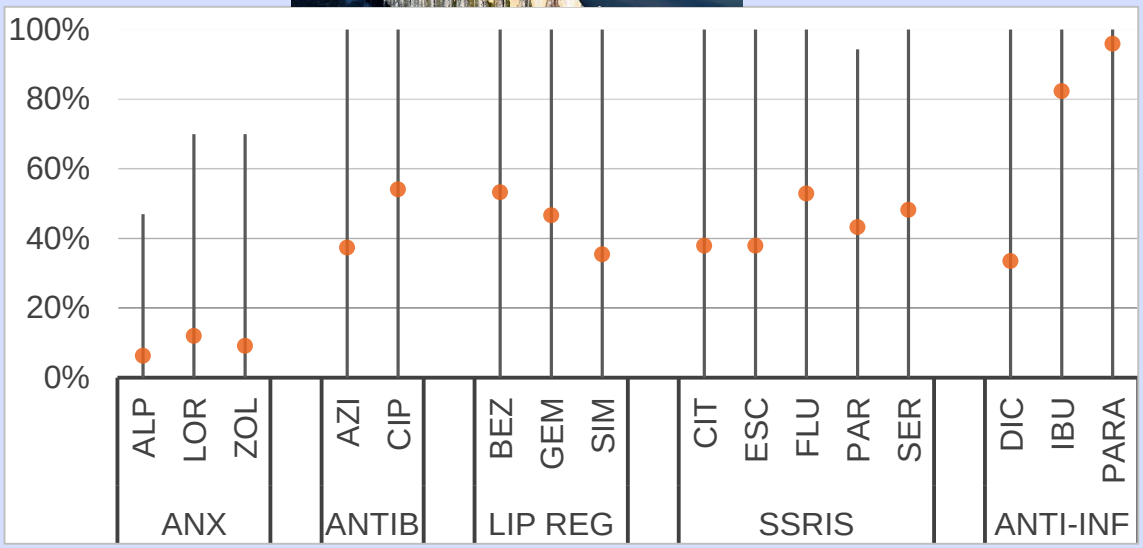
Excretion

- Excretion of the parent compound and conjugates (glucuronide and sulphate)
- Differences are explained by genomically distinct metabolizing capacities
- SSRIs were the therapeutic group with lower excretion rates



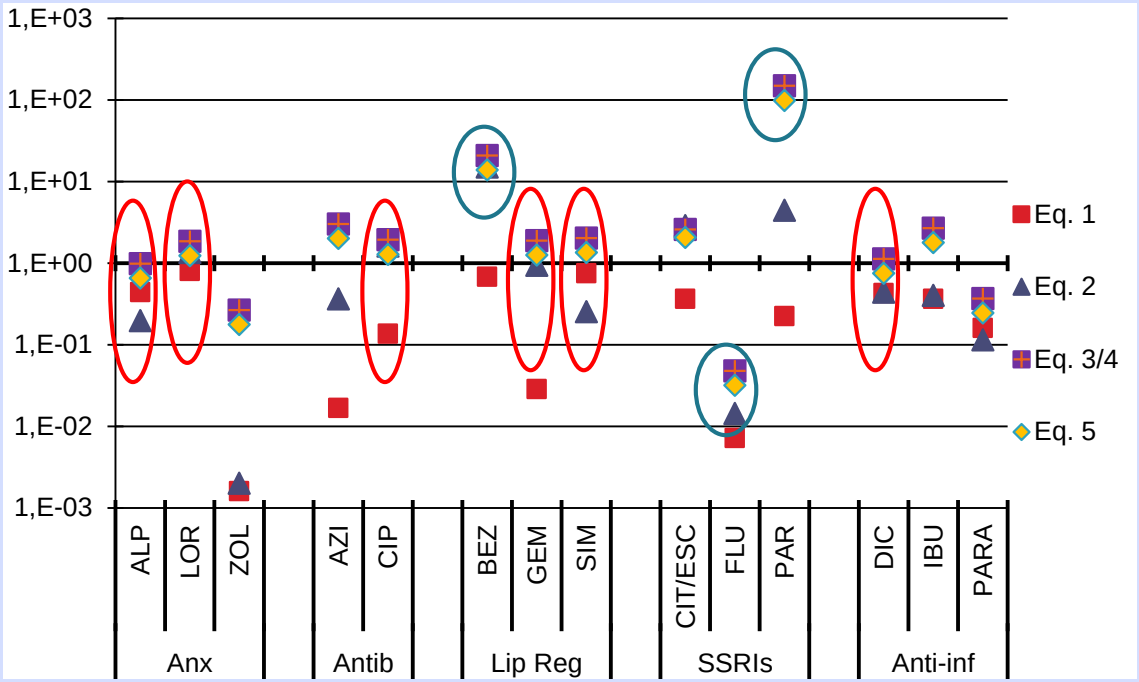
Removal efficiencies and volume of wastewater

- Lower averages for anxiolytics
- All pharmaceuticals had at least one report with 0% removal
- Variation occur due to different operation conditions and served population
- Volume of wastewater produced by the Portuguese population 133L/inhab/day



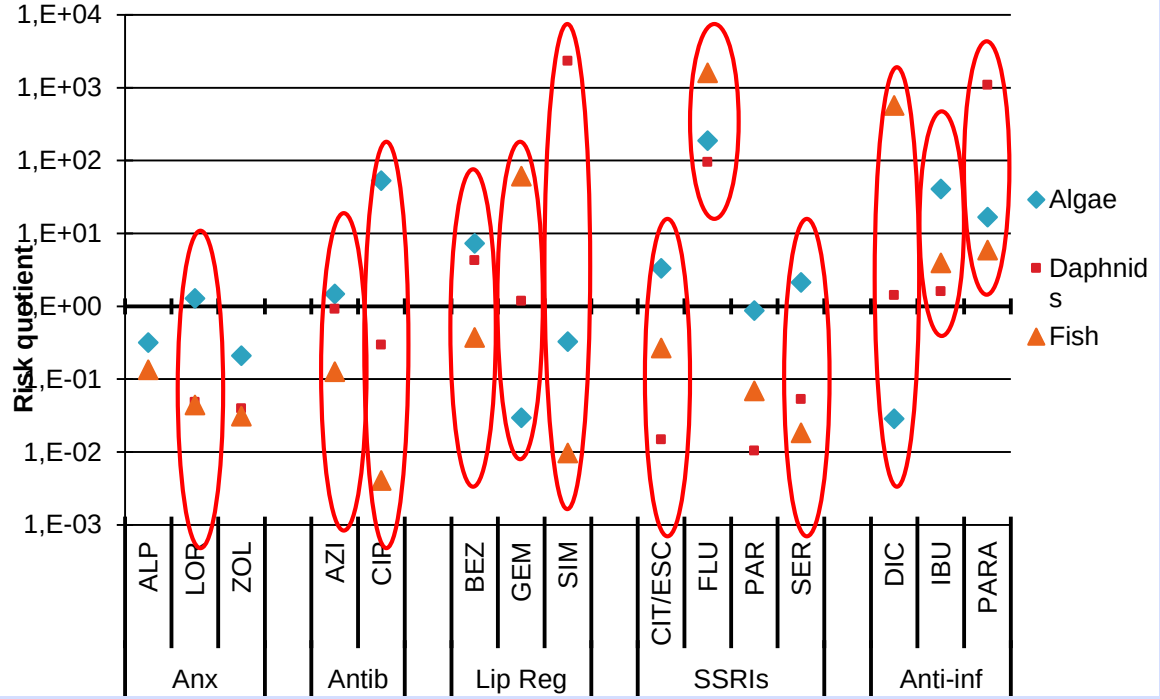
Ratio between MECs and PECs in WWE

- Inverse modelling
- Eq. 3 presented the lowest standard deviation average
- BEZ, FLU and PAR had factors higher than 10
- Inclusion of a safety factor of 10 in Eq.3



Risk quotients calculated as the ratio between PECs in WWE and PNECs

- Eq. 3 with a safety factor of 10
- 12 pharmaceuticals had RQ higher than 1
- Using PECs in surface water 7 still have RQs higher than 1



Conclusions

Conclusions

- 9 out of the 16 pharmaceuticals had penetration rates higher than the default value, therefore, the default value of Fpen, should be updated.
- Using the worst case scenario results, all of the selected pharmaceuticals did not present any removal.
- From the five equations assessed Eq. 3 gave the best results.
- Additionally each five years, after new therapeutic indications or increased consumption the ERA should be carefully reviewed.
- ERA should incorporate the risk-benefit analysis.
- Using PECs in surface water, 7 pharmaceuticals still have RQs higher than 1.

Acknowledgments

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