Science-based trigger for the terrestrial assessment of human pharmaceuticals

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Abstract

Current environmental risk assessments (ERA) for human pharmaceuticals focus primarily on the risks to the aquatic environment(1). Sewage sludge from waste water treatment plants (WWTP) is often used as fertiliser; consequently, there may also be exposure to terrestrial environments for active pharmaceutical ingredients (APIs) which adsorb significantly to sewage sludge. In the updated draft guidance document(2), the EMA recognise that, in addition to adsorption, high concentrations in the WWTP have the potential to drive risk in the terrestrial environment. The guidance proposes a combined trigger incorporating both PECsw (surrogate for concentrations entering WWTPs) and Koc (adsorption). The present study examines existing terrestrial toxicity data to demonstrate a scientific basis for an alternative approach, based on a PECsoil action limit (≥0.1 mg/kg), for triggering terrestrial ERAs.

Introduction

- Aquatic ERA for human medicinal products(1) and terrestrial ERA for veterinary medicines(3) utilize exposure based triggers to prioritize testing and assessment.
- Recent proposed draft triggers from EMA lack a clear science-based justification
- Data generated since 2006 under current human medicines guidance were collated from publicly available EPARs and internal company databases
- The data is examined to establish the scientific basis for a PECsoil action limit.

Methods

- Data from 40 Active Pharmaceutical Ingredients (APIs) were collated from publicly available EPARs or from internal company databases of participating companies.
- A full terrestrial ecotoxicity dataset was available for 35 APIs; investigating effects on soil micro-organisms (SMO), terrestrial plants, earthworm and collembola. The remaining APIs had one or more studies
- In total 147 individual study endpoints were available for investigation and PNEC derivation
- PNECs were calculated based on NOECs or EC_{10} for each study according to current guidance by applying an appropriate safety factor (10) to the endpoint(2)
- No assessment factors were applied to SMO studies, the guidance(2) states:
  "An assessment factor is not relevant to this endpoint – when the difference in rates of nitrate formation …is equal to or less than 25% at any sampling time before day 28, the active ingredient can be evaluated as having no long-term influence on nitrogen transformation in soils.
- The distribution of PNECs were analyzed for each PNEC individually and also based on collective data for APIs

Special note on soil micro-organism test

- *Soil micro-organism test (SMO; nitrogen transformation test) represent a special case were the study design limits the utility of the data in this analysis*
  - *SMO studies are often designed to test the effects of 1 and 5 or 10 x the PECsoil*
  - *The PECsoil values for pharmaceuticals are often very low and the studies regularly result in no effects at the highest concentration tested*
  - *PNECs from historic SMO studies therefore may represent a significant source of conservatism as in this analysis*

Results

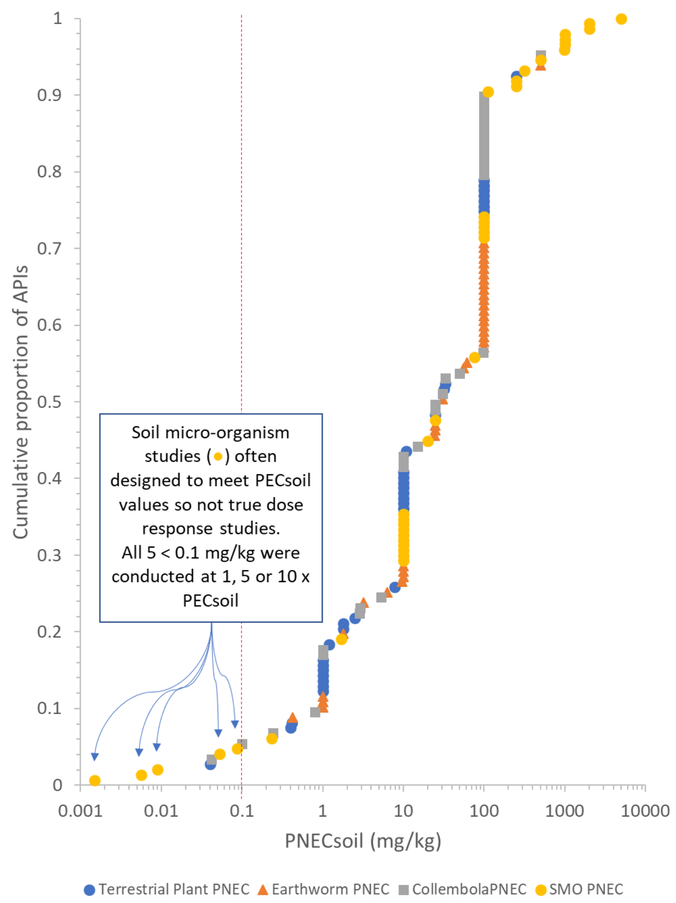
Table 2 Descriptive statistics on data collected

	Soil micro-organism	Terrestrial plants	Earthworm	Collembola
Total available PNECs	37	35	39	36
Lowest API PNEC	9	15	5	11
Lowest API PNEC (exc. SMO)	N/A	17	6	16
PNEC ≤0.1 mg/kg	5	1	0	2
% PNECs ≤0.1 mg/kg	|----------5%*----------|			
	N/A	|----------3%**----------|		

(*) Including SMO studies (n=147); (**) Excluding SMO studies (n=113)

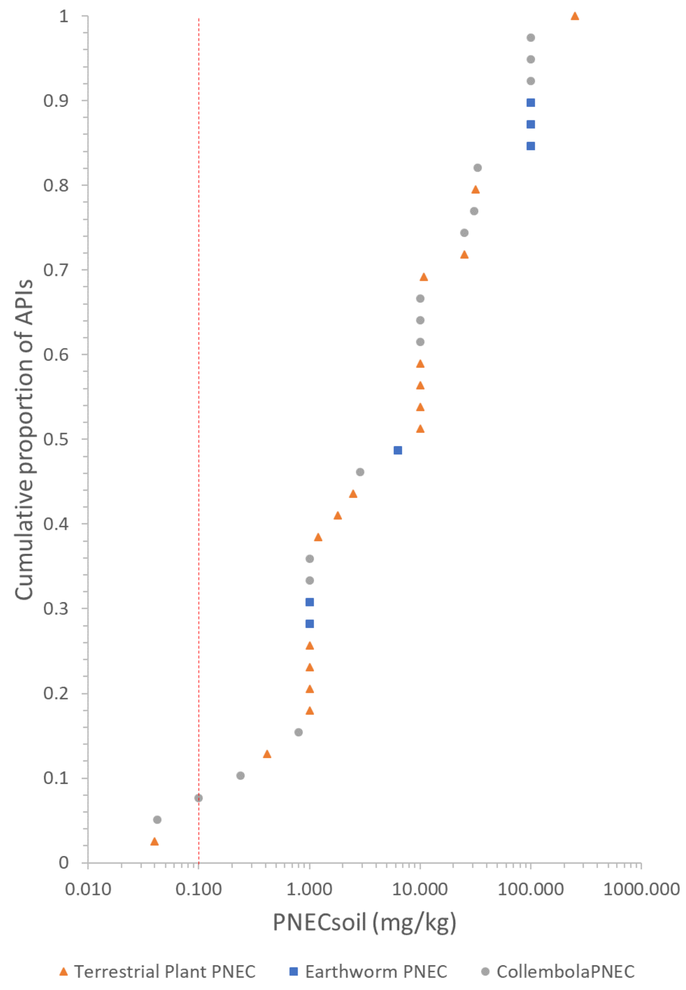
- When examined independently a dataset of 147 PNECs could be calculated.
- Of these only 8 PNECs (5%) would be below the proposed PECsoil action limit of 0.1 mg/kg
  - **95% of all PNECs were above 0.1 mg/kg**
- SMO studies were found to be unique in that in almost all cases the tested concentrations were chosen based on the PEC of the API.
  - All of the 5 SMO PNECs below 0.1 mg/kg were based on (or above) the PEC
  - Therefore no risk was identified (limit test)

Figure 1 Distribution of Terrestrial PNECs (n=147)
Red line = proposed PECsoil action limit (0.1 mg/kg)



- If SMO studies are removed from this analysis (due to design limitations) 113 PNECs remain in analysis and:
  - **97% of PNECs were above 0.1 mg/kg**
- If the lowest PNEC of each API is examined a similar picture emerges:
  - **80% of APIs (32/40) have a lowest PNEC >0.1 mg/kg**
  - **When excluding SMOs: 92.5% of APIs (36/39) have a lowest PNEC >0.1 mg/kg**

Figure 2 Lowest API PNEC excluding SMOs (n=39)
Red line = proposed PECsoil action limit (0.1 mg/kg)



Conclusions

- A database of 147 endpoints from 40 APIs was examined.
- Even considering highly conservative PNECs from soil micro-organism studies, **95% of all terrestrial PNECs are >0.1 mg/kg**
- **A PEC action limit of ≥0.1 mg/kg soil is proposed as a trigger for terrestrial ERA for human medicinal products.**
- Implementation of such an approach is protective and in-line with both existing aquatic guidance for human medicines(1), and veterinary medicine guidance for terrestrial assessments(3).
- Further investigations are proposed examining impact of pharmacological mode of action and comparing these effects data with the EU default PECsoil and consumption based PECsoil values.

References

1. CHMP 2006. Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/SWP/4447/00 corr. 2
2. CHMP 2018. Guideline on the environmental risk assessment of medicinal products for human use; EMEA/CHMP/SWP/4447/00 Rev. 1
3. CVMP 2000. Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I; CVMP/VICH/592/98-FINAL.

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