Investigating the Impact and Scientific Justification Behind Changes to Groundwater Risk Assessment of Human Pharmaceuticals

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Abstract & Introduction

One aspect of the proposed revision to the European Medicines Agency (EMA) Environmental Risk Assessment (ERA) guidance is the inclusion of additional precautionary measures for the assessment of risk to groundwater organisms. This involves the revision of the groundwater assessment from a specific invertebrate assessment (utilising the *Daphnia* endpoint for PNEC derivation) to a conservative assessment of all taxa irrespective of their relevance to groundwater along with an additional safety factor (PNECsw / 10). Little scientific justification is provided to warrant such a change but the change is more precautionary.

Here the data for registered Active Pharmaceutical Ingredients (APIs) are collated and the RQ according to current and revised ERA guidance are analysed. The aim is to quantify the impact of the revised groundwater risk assessment, understand if it is warranted or justifiable, and determine whether the proposed change assists researchers in understanding the risks of human pharmaceuticals.

Methods

- Consumption (EU country with the highest per capita use) and Defined Daily Dose (DDD) data from APIs were collated from 2 recent analyses[3,4], and/or the WHO DDD index[5].
- Surfacewater (sw) and groundwater (gw) PECs & PNECs were derived following existing and revised EMA ERA guidance[1,2].
- PECs were calculated according to the EMA guidance using both commercial consumption data (n=131) and DDDs (n=101) to estimate the impact on default (DDD) and refined (consumption) assessments

Table 1 Summary of data used for PEC and PNEC derivation under relevant guidance

Defined Daily Dose	PECsw	PECgw	PNECsw	PNECgw
Current EMA Guidance 2006	DDD & Default Fpen (0.01)	PECsw x 0.25	Lowest available NOEC / 10	Daphnia NOEC / 10
Revised draft EMA Guidance 2018		PECsw x 0.25	Lowest available NOEC / 10	PNECsw / 10
Consumption	**PECsw**	**PECgw**	**PNECsw**	**PNECgw**
Current EMA Guidance 2006	Highest per captia consumption data from EU country	PECsw x 0.25	Lowest available NOEC / 10	Daphnia NOEC / 10
Revised draft EMA Guidance 2018		PECsw x 0.25	Lowest available NOEC / 10	PNECsw / 10

Data analysis

- These data were then used to conduct groundwater risk assessments allowing a comparison of:
  I. The Risk Quotients (RQs) across the existing and draft revised guidance documents
  II. The relationship between surface- and ground- water risk assessments
  III. Relative impact of refined and default groundwater RQs (RQgw)
- Conclusions on the potential impact of the revisions to the groundwater risk assessment, needs for risk refinement and risk mitigation including labelling

Results

- The comparison of groundwater RQ values are shown in Figure 1 and 2.
- **RQgw under the revised guidance are increased between 10- and 73million-fold (Figure 1)**
- APIs which show a 10x increase are those where PNECsw is driven by *Daphnia.*
- APIs which show a >10x increase are driven through specific sensitive species (i.e. fish or 'algae')
- Specifc MoAs dominate top 20 increases
- **RQgw <u>always</u> = 2.5 x RQsw (Figure 2)**

Figure 1 Distribution showing the fold-change between 2006 and 2018 RQgw (consumption data; n=131)

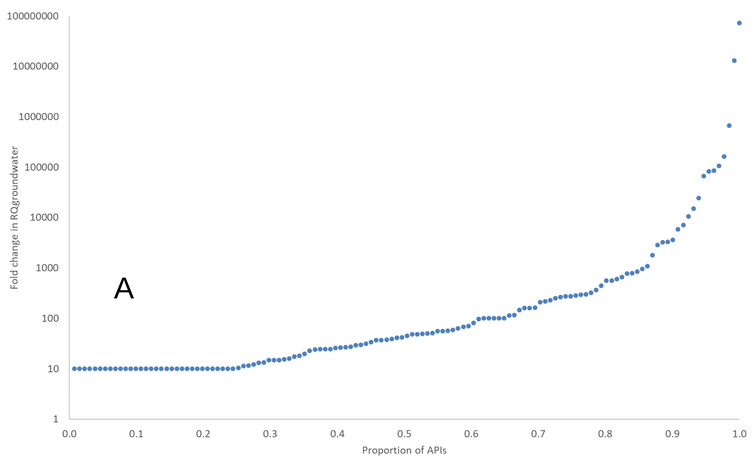


Figure 2 Distribution of RQgw and RQsw between 2006 and 2018 (consumption data; n=131 APIs)

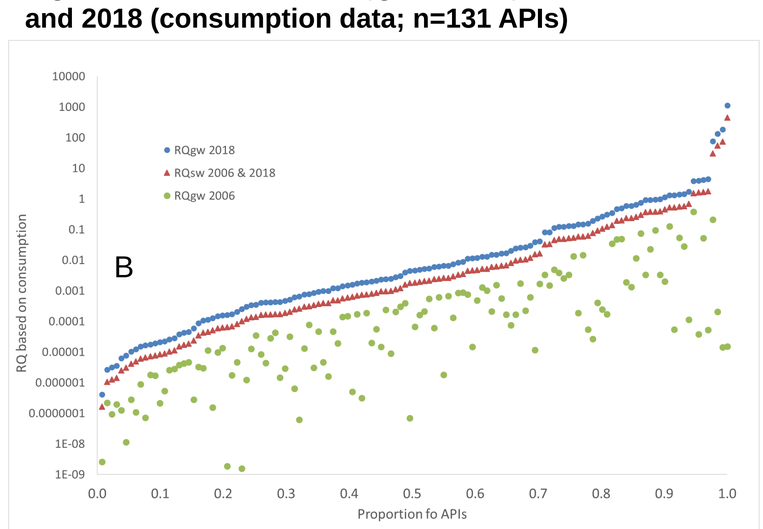
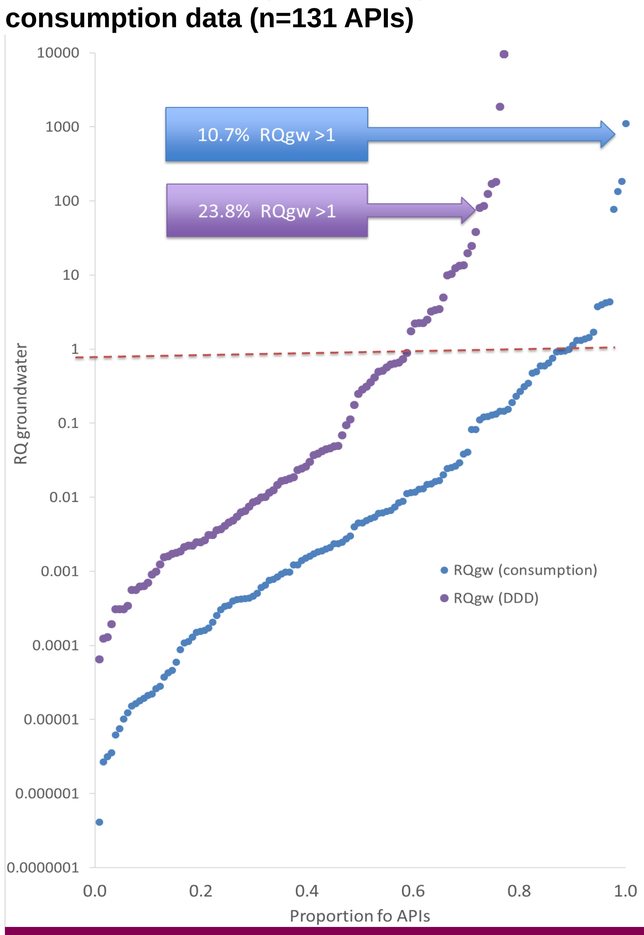


Table 2 Top 20 API increases in RQgw from 2006 – 2018 (consumption data; n=131)

API Name	Mode of Action	Fold-change between 2006 and 2018 RQgw	Endpoint driving the PNEC
Tigecycline	glycylcycline antibiotic	955	FISH
Lapatinib	Kinase Inhibitor	1080	FISH
Quetiapine	Dopamine / serotonin receptor antagonist*	1800	FISH
ceftriaxone	Beta-lactam antibiotic	2850	ALGAE
Anastrozole	Anti-oestrogenic aromatase inhibitor	3200	FISH
Betamethasone	Corticosteroid	3269	FISH
Linezolid	Oxazolidinone antibiotic	3582	ALGAE
Ertapenem	carbapenem antibiotic	5857	ALGAE
Ceftazidime	Broad-spectrum Antibiotic	7076	ALGAE
Brimonidine	alpha-adrenergic agonist	10526	FISH
Regorafenib	Kinase inhibitor	15000	FISH
Mometasone	Corticosteroid	24286	FISH
Ceftaroline	cephalosporin antibacterial	65833	ALGAE
Fulvestrant	Oestrogen receptor antagonist / degrader	82456	FISH
Doripenum	carbapenem antibiotic	85455	ALGAE
Ampicillin	Broad-spectrum antibiotic	105172	ALGAE
Ceftobiprole	cephalosporin antibiotic	160870	ALGAE
Estradiol	Natural hormone	666667	FISH
Ethinylestradiol	Synthetic hormone	12900000	FISH
Levongesterol	Synthetic hormone	72900000	FISH

Figure 3 Distribution of RQgw values calculated with "default" DDD data (n=101 APIs) and "refined" consumption data (n=131 APIs)



Discussion & Conclusions

- Revised EMA groundwater assessment would result in increased frequency of predicted groundwater risks
  - Increase varies from 10x – 72900000x
  - Potential for groundwater risk now common and would drive risk refinement requirements
  - This revised risk is driven by organisms with less ecological relevance to ground water (e.g. fish and phototrophic algae)
  - Risk is highest for those pharmaceuticals with specific MoAs (e.g. those active against the sex steroid axis and antibiotics)
- The RQgroundwater will always be 2.5 x higher than the RQsurfacewater (figure 2)
  - This is in danger of rendering the surfacewater risk assessment redundant
  - Traditional approaches to refining the risk assessment may be less applicable to groundwater
  - The use of consumption data for worst case exposure assessment (100% patient use, no metabolism and no removal in sewage treatment) shows potential for initial refinement of these risks (Figure 3).
  - Further refinement may requirement revision to surface water exposure
- There is a lack of data confirming or refuting the potential risk or impacts of pharmaceuticals to groundwater organisms. More data is needed on species diversity, relative sensitivity, mode of action conservation, and on the actual exposure to species in these environments.
- This analysis demonstrates that the proposed change in the groundwater ERA has significant impacts but the ecological basis is unclear and unjustified. This change is in danger of:
  1. Rendering the surfacewater water risk assessment of pharmaceuticals redundant.
  2. Moving research resource towards an uncertain and unsubstantiated groundwater risk
  3. Increasing testing and labelling demands on human pharmaceuticals with little evidence of increased environment protection

References

1. CHMP 2006. Guideline on the environmental risk assessment of medicinal products for human use
2. CHMP 2018. Guideline on the environmental risk assessment of medicinal products for human use
3. Gunnarsson L., et al., 2019. Pharmacology beyond the patient – The environmental risks of human drugs. *Environment International.* **129** 320-332
4. Tell J et al., 2019. Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. *Integrated Environmental Assessment and Management* 15 **(3)** 312-319
5. WHO ATC/DDD Index (https://www.whocc.no/atc_ddd_index/)

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