A Cocktail a Day Keeps the Doctor Away?

How to Consider Potential Additive Mixture Toxicology within Veterinary Pharmaceutical Legislation

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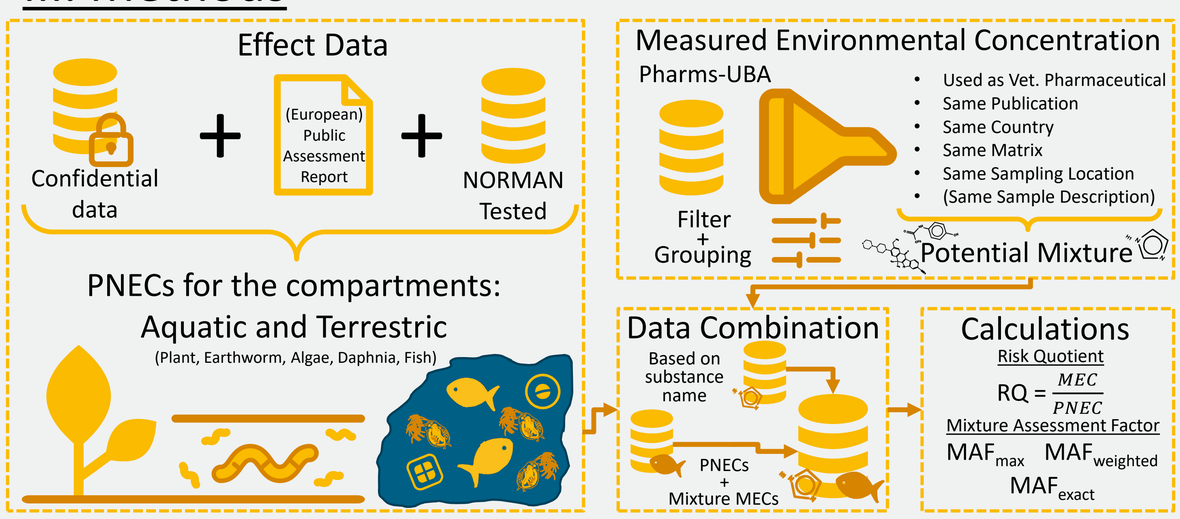
I. Introduction

This study assesses how a MAF might be defined for pharmaceuticals, **based on 'real world' data**, considering the extensive variety of mixtures possible, and what role single-substance tests and MECs can play in this process. While conventional ecotoxicological assessments typically **focus on single compounds**[1,2], the REACH regulation has **demanded a MAF** for some time[3]. Therefore, MAF_{max}, $MAF_{weighted}$, and MAF_{exact} were calculated, based on **real-world RQs**, and an applicable **MAF for veterinary medicines** EIA/ERA was suggested.

II. Research Questions

Q1: Which mixtures are found in the environment, and in what range are the additive MECs?
Q2: Are there any substances and mixtures that raise concerns about potential real world RQs based on RQ_{real} = MEC/PNEC?
Q3: Which MAF_{max}, $MAF_{weighted}$, and MAF_{exact} can be derived?
Q4: Based on additive effects, on what level a potential general applicable $MAF_{suggest}$ should be set?

III. Methods



The approach includes **publicly available databases**, such as the PU for MECs and the (European Medicines Agency's) public assessment reports for effect data. Those were **supplemented by internal data** from the German Environment Agency. Afterwards, **data where grouped to derive potential mixtures** and combined with associated PNECs. RQs and MAFs were derived (Fig. 1) in the last step. The $MAF_{suggest}$ is defined as median of all MAFs ≥ 1 (Tab. 1).

IV. Results

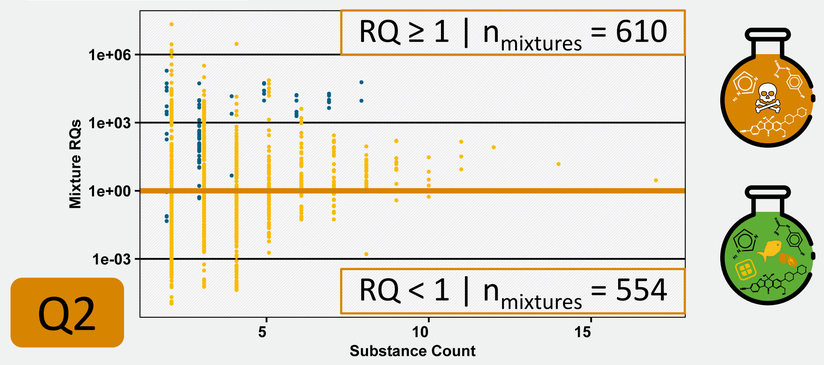


Figure 1: Mixture Risc Quotients as the sum of the substance RQs per mixture, divided by compartment.

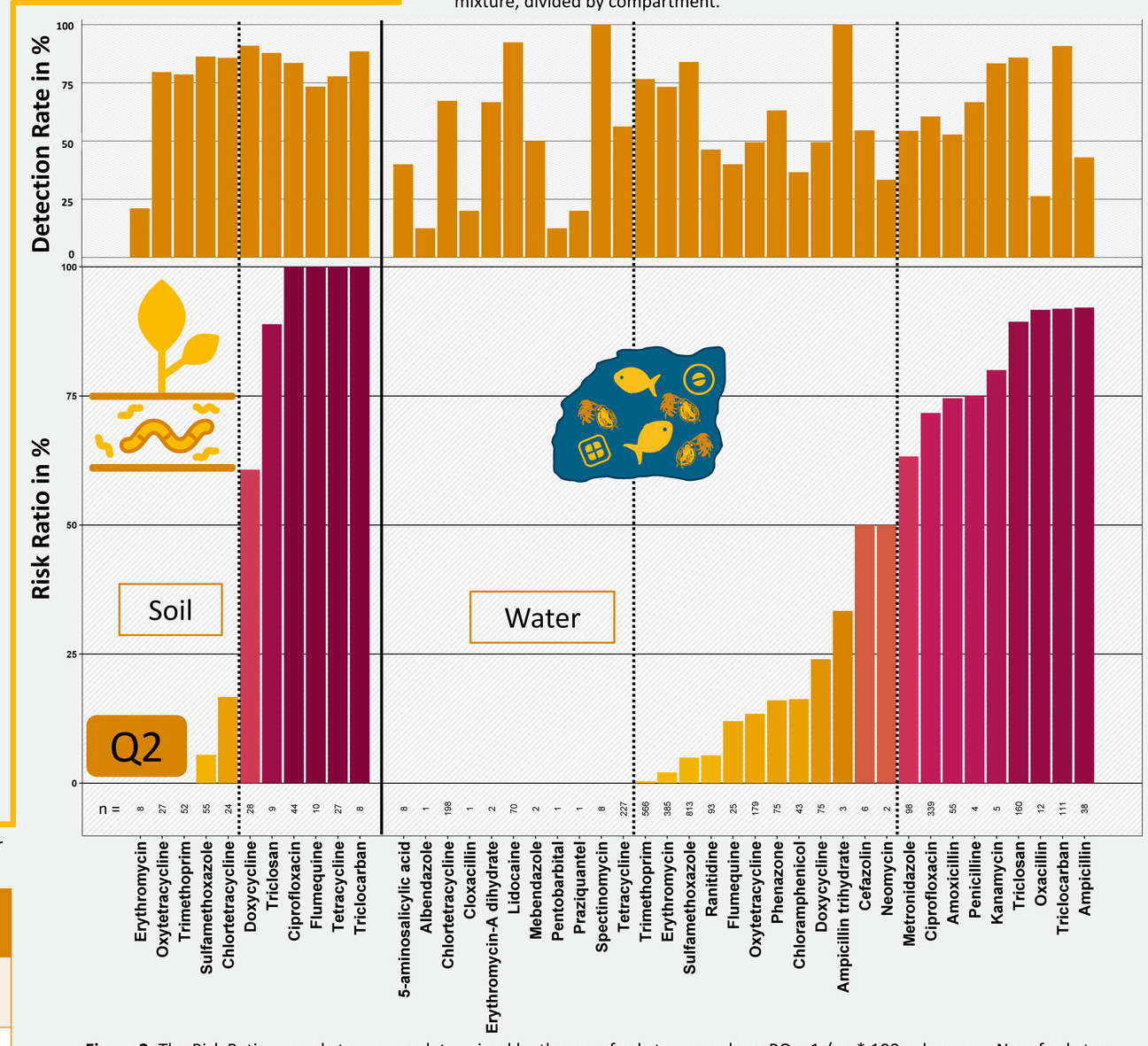


Figure 2: The Risk Ratio per substance was determined by the no. of substance x where RQ > 1 / n_x * 100, where n_x = No. of substance x detections and the corresponding detection rate, divided by compartment.

Table 1: Results of the MAF calculations based on different methods. The minimum, mean and maximum MAFs per compartment are displayed, along with a deviated $MAF_{suggest}$ for potential incorporation into regulatory guidelines.

Q3/Q4	MAF_{exact} [4]	MAF_{max} [4]	$MAF_{weighted}$	$MAF_{suggest}$
	Min | Mean | Max	Min | Mean | Max	Min | Mean | Max	Median
Soil	1.1 | 2 | 5.2	1.5 | 10^3 | 10^5	42 | NA | NA	~ 5
	Min | Mean | Max	Min | Mean | Max	Min | Mean | Max	Median
Water	1.1 | 1.7 | 7.3	1.01 | 15 | 10^8	1.1 | 11.5 | NA	~ 2.5

The **effect dataset contained 51 AS**, which can theoretically form 4.22 x 10^{66} different partial mixtures. The **PU MEC database shows that 34 different AS** can be found with theoretical 8.03 x 10^{38} mixtures possible. 219 cases were identified, where different mixtures occurred in the environment. In total, **1164 mixtures** (Fig. 1) within approx. **6600 valid data points**, where found. Mixture sizes ranged from 2 to 17 with additive MECs from ng up to mg/kg soil or mg/l water. Risk drivers with high risk ratios and detection rates were for example Triclocarban, Triclosan or Ciprofloxacin in water and Tetracycline additionally in soil (Fig. 2). A **suitable MAF** for incorporating mixtures **may fall within 2.5 to 5** (Tab. 1).

V. Conclusion

Mixtures in the environment are a cause for concern and should be addressed in EIA/ERA!

Our analysis of **veterinary and dual-use AS** highlights the need for an extra safety factor due to already elevated mixture exposure. This suggests a **similar approach for human pharmaceuticals**, identifies relevant mixtures, risk drivers (Fig. 2), their occurrence, risk potential (Fig. 1), and possible regulatory adaptations (Tab. 1) to align with environmental protection goals.

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VI. Literature

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3. Treu, G., Schulze, J., Galert, W., & Hassold, E. (2024). Regulatory and practical considerations on the implementation of a mixture allocation factor in REACH. Environmental Sciences Europe, 36(1), 101. https://doi.org/10.1186/s12302-024-00910-z
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VII. Abbreviations

MAF	Mix. Assessm./Alloc. Factor
MEC	Meassured Environ. Conc.
RQ	Risc Quotient
PNEC	Predicted No Effect Conc.
EIA/ERA	Env. Impact/Risc Assessm.
PU	Pharms UBA Database
AS	Active Substance

Umwelt Bundesamt