# Out of Sight?

## Evaluation of the Current Phase I Action Limit for Assessing Environmental Impact of Veterinary Pharmaceuticals

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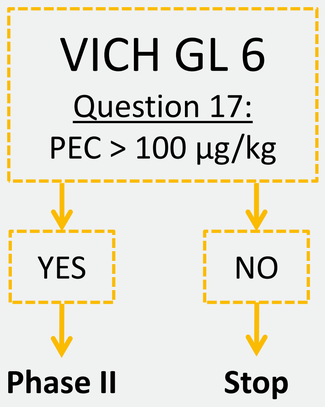
## I. Introduction

The **VICH GL 6**[1] on ecotoxicity outlines a tiered assessment scheme that is mandatory for all active substances (AS) used in **veterinary medicinal products** (VMP). In question 17, the predicted environmental concentration (PEC) of the AS is compared to a **action limit** (AL) of 100 µg/kg for soil. If PEC > AL, the VMP enters Phase II[2]. This AL is currently based on data that were recorded from 1973-1997 in the USA[3]. Due to additional authorizations of **new AS** with **higher efficacy** and **type II** variations, extensions or generics[4] since then, a **review** of the action limit seems necessary.

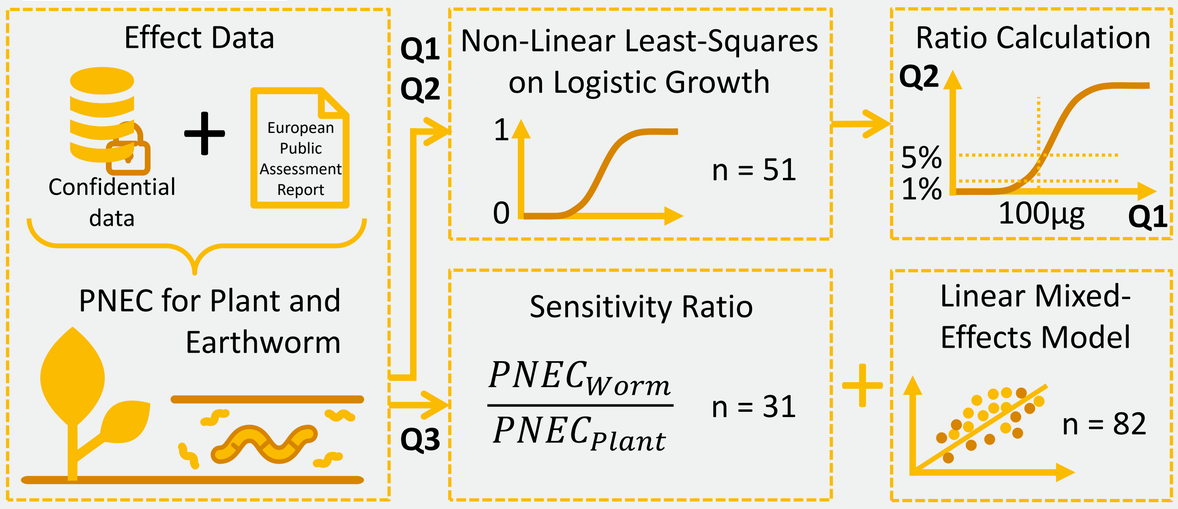



## II. Aim

It should be **clarified** whether the **action limit** still **fulfils** its role as a precautionary decision **criterion** for veterinary pharmaceutical legislation, determining whether an experimental/in-depth **Phase II** environmental impact assessment (EIA) must be conducted. For this, all effect data for AS that entered a **Phase II, terrestrial Tier B** EIA where obtained. So, the following questions arose:

1. Is the Environmental Impact Assessment **Phase I action limit of 100 µg/kg** soil **still appropriate** or does it need to be redefined?
2. If it needs to be redefined, **where** should the action limit be set to **minimize the impact** on the environment to an appropriate degree?
3. How significant are the **differences** in sensitivities **between the organisms** plant (OECD 208) and earthworm (OECD 220/222)?

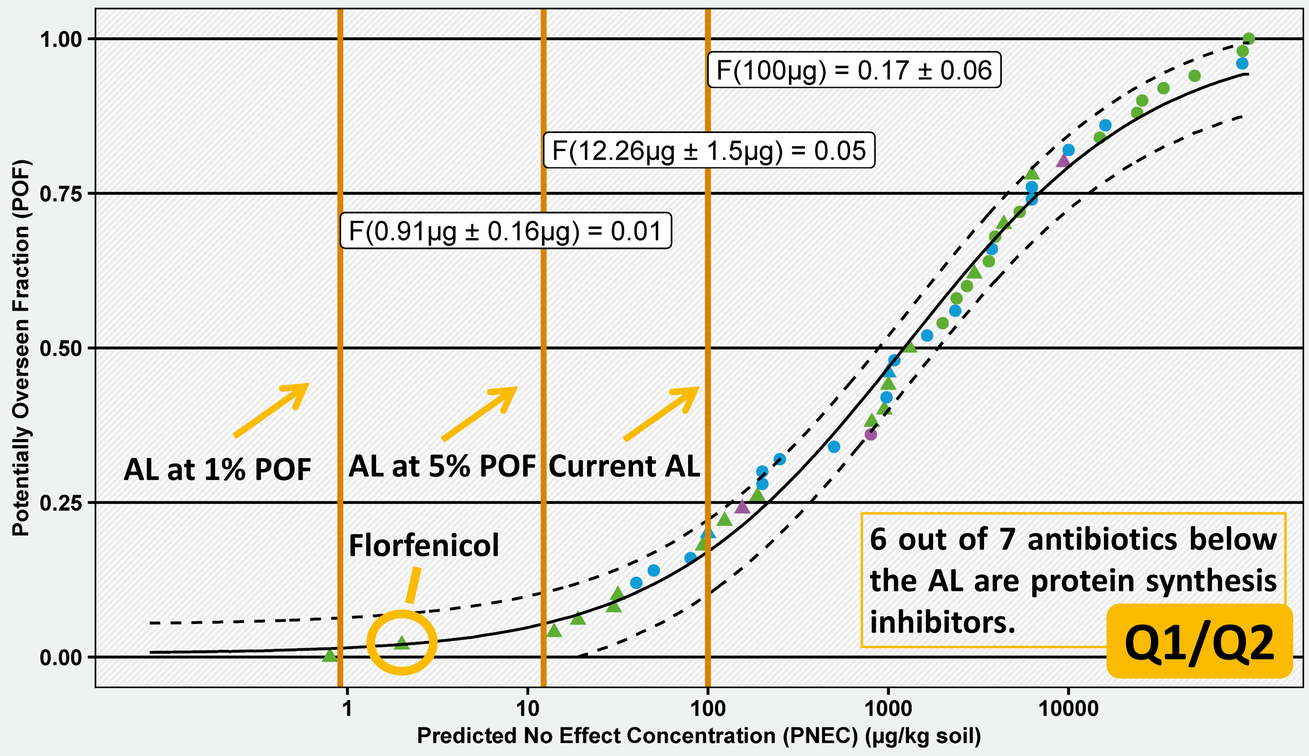
## III. Methods

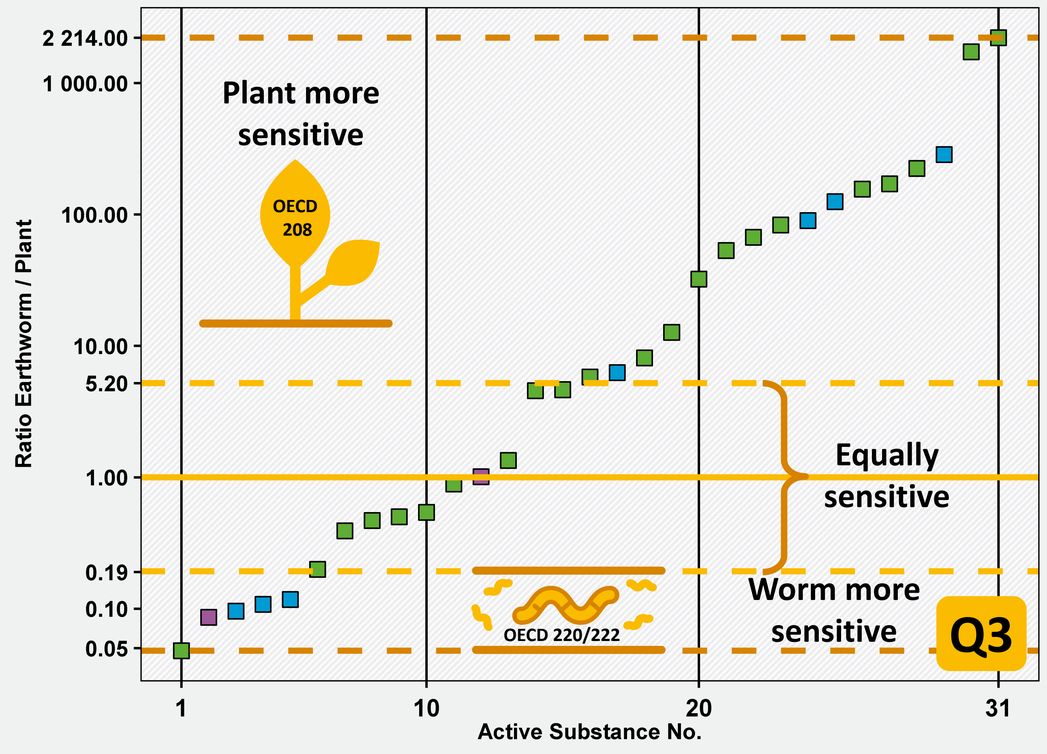



The most sensitive **Phase II effect data** endpoints from plants and earth worms were used. In total, effect data were **available for 51 AS**, of which **31** were identified, where **both earthworm and plant** endpoints were available. Collembola and N-Transformation tests were excluded from the analysis due to lack of relevance to the AL and limited comparability with plant/earthworm tests, partly due to tailored approaches.

## IV. Results


| Characteristic | N | Beta | 95% CI | P-Value |
|---|---|---|---|---|
| **Species** | 82 | 2.6 | 1.3 - 4.0 | < 0.001 |
| **Plant** | 34 | | | |
| **Worm** | 48 | | | |




## V. Results and Discussion

The analysis shows that the **AL may be inappropriate** to fulfil its role in sufficient environmental risk reduction. For a reduction to **5%** probability of missing a potentially toxic substance, a more appropriate AL might be **10 times lower** (10 µg/kg soil). For **1%**, the AL needs to be reduced by a **factor of approximately 100** (1 µg/kg soil). Schwarz et al.[5] state that the AL for human drugs falls within the range of 1% and 5%. Based on species sensitivity (in **Q3**), the **plant** is, on average, **statistically significantly more sensitive** than the earthworm.

## VI. Conclusion

### The action limit is not sufficiently protective.

The results suggest that the **action limit** is only fulfilling its role to a **limited extent.** Currently, the potentially overseen fraction is **approximately 20%**. Therefore, the aim should be to **reduce** the action limit to an appropriate level, to **include antibiotics** in question 16 (‘**however**’) or introduce a **tailored approach** based on mode of action.

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## VII. Literature

1. EMA. (2000). CVMP/VICH/592/98-FINAL - guideline on environmental impact assessment (EIAS) for veterinary medicinal products—Phase I. European Medicines Agency.
2. EMA. (2004). CVMP/VICH/790/03-FINAL - guideline on environmental impact assessment for veterinary medicinal products phase II. European Medicines Agency.
3. AHI – ERA WP. (1997). Analysis of Data and Information to Support a PEC Soil Trigger Value for Phase I – Data from the United States from 1973–1997. Animal Health Institute.
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5. Schwarz, S., Gildemeister, D., Hein, A., Schröder, P., & Bachmann, J. (2021). Environmental fate and effects assessment of human pharmaceuticals: Lessons learnt from regulatory data. Environmental Sciences Europe, 33(1), 68. https://doi.org/10.1186/s12302-021-00503-0