Out of Sight?

The Insufficiency of the Phase I Action Limit in Veterinary Early Impact Assessment

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I. Introduction

The **VICH GL 6**[1] about 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 in question is compared to a so-called **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 authorization of **new AS** with **higher efficacy** and **type II** variation, extension or generics[4] since then, a **review** of the action limit seems necessary.

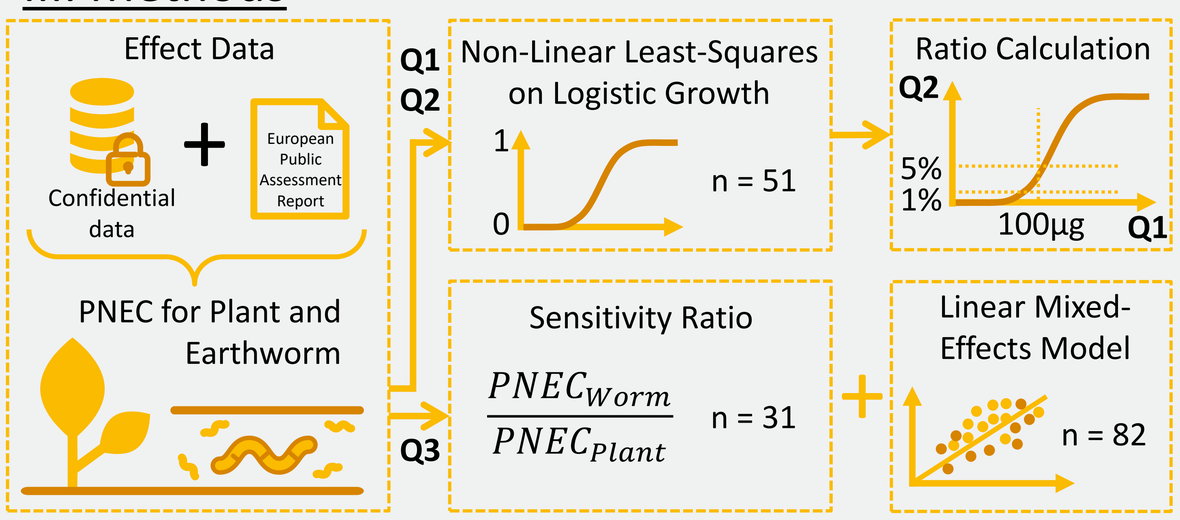
VICH GL 6
Question 17:
PEC > 100 µg/kg
YES → **Phase II**
NO → **Stop**

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** to 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

Based on the model results above, **Q1/Q2** can be answered as follows: the **AL may be inappropriate** to fulfil its role in sufficient environmental risk reduction. In addition, the model shows that for a **5%** probability of missing a potentially toxic substance, a more appropriate AL might be **10-20 times lower** (5-10 µg/kg soil). For **1%**, the AL needs to be reduced by a **factor of approx. 200** (0.2-0.6 µg/kg soil). 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**. At present, the calculated risk of **failing** to identify potentially harmful substances is **approx. 20%**. The aim should therefore 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

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