



Environmental risk assessment of veterinary medicines A new concept for a plant test with a more realistic exposure scenario

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Introduction

Environmental effects of veterinary medicines are assessed according to the guidelines of the European Medicines Agency (EMA) and the VICH GL 38 (1). A terrestrial plant test in phase II is required because residues of pharmaceuticals release with manure from treated animals on agriculture land. The current regulations take into account only the parent compound but do not consider transformation products and NER (Non Extractable Residues). This might result in an incorrect estimation of risk in case of substances applied on agricultural soils with manure. Therefore the German Federal Environment Agency has initiated a research project to develop a special terrestrial plant test with a more realistic exposure scenario. This new approach is currently developed with different plant species, different manures and storing periods by two research partners Fraunhofer IME Schmallenberg and ECT Oekotoxikologie GmbH Flörsheim.

Standard Approach

Phase II, Tier A: Plant test according to OECD Guideline 208: Seedling Emergence and Seedling Growth Test (2)
Using the EC₅₀ values of the plant test according to OECD 208 (1; 3)
Testing of 6 species: Reflection paper on testing strategy and risk assessment for plants (3)

Phase II, Tier B: Using the NOEC or EC₁₀ values of the plant test according to OECD 208 (1; 3)
If PEC/PNEC ≥ 1 in Tier B : No tests available

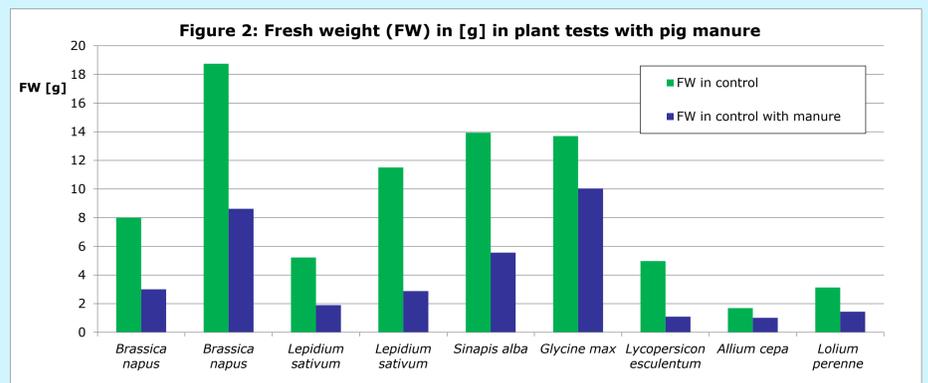
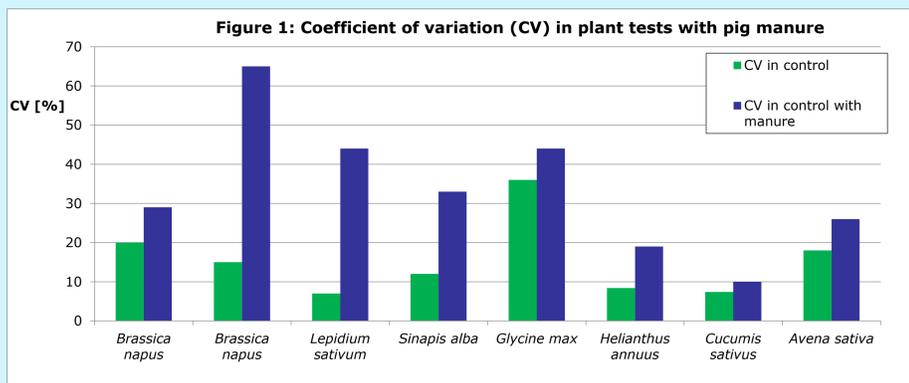


Special Plant Test with manure

In the plant test with a more realistic exposure scenario the substance is applied in manure and stored under anaerobic conditions over a defined period prior to testing. Then this mixture is tested in a standard terrestrial plant test according to OECD 208.

The following problems are occurring in plant tests submitted by applicants:

- Coefficient of variation in controls with manure partially significantly higher than in controls without manure (Figure. 1)
- No clear dose-response relationship for some plant species
- Growth in controls with manure partially significantly lower than in controls without manure (Figure. 2)



Optimisation of the Plant Test

UBA- Research project „Development of a concept for a plant testing approach for veterinary pharmaceuticals“ (FKZ 3711 63 424)
Duration: 2011 - 2013

Objective: Development of a special terrestrial plant test with a more realistic exposure scenario with manure

Research Partner: Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Auf dem Aberg 1 57392 Schmallenberg and ECT Oekotoxikologie GmbH (ECT), 65439 Flörsheim

These Questions leading to following Experiments

Are terrestrial plant tests with soil/manure mixtures more variable than plant tests with standard soil?



Controls without manure and controls with manure are tested. The results are compared.

Does the manure content itself in the soil (without addition of test substance) influence the growth of different plant species? Are there appropriate/ inappropriate test species?



Preliminary tests with eight test species in pig and cattle manure are conducted. Five concentrations in the range of 26 to 170 kg Nitrogen/ha (equivalent to 7 to 46 g manure/kg soil) are tested.

Can changes in the sensitivity of plant species be observed in terrestrial plant tests with manure?



Two antibiotics are tested with six plant species from five different plant families in pig and cattle manure.

How does the manure storage time influence the phytotoxicity?



Tests without storage of manure, with half-maximal and maximal storage time (incubation under anaerobic conditions) are conducted.

How many replicates should be tested at a minimum?



Terrestrial plant tests are conducted with eight replicates.

Are specific statistical methods necessary like methods taking into account high variance?



Evaluation of the test results with different statistical methods.

References:

- VICH. Guideline on Environmental Impact Assessment for Veterinary Medicinal Products Phase II. London: CVMP/VICH/790/03-Final
- OECD 208: OECD Guidelines for the Testing of Chemicals, Terrestrial Plant Test: Seedling Emergence and Seedling Growth Test, Adopted 19.07.2006
- Reflection paper on testing strategy and risk assessment for plants: EMA/CVMP/ERA/147844/2011



Incubation of manure