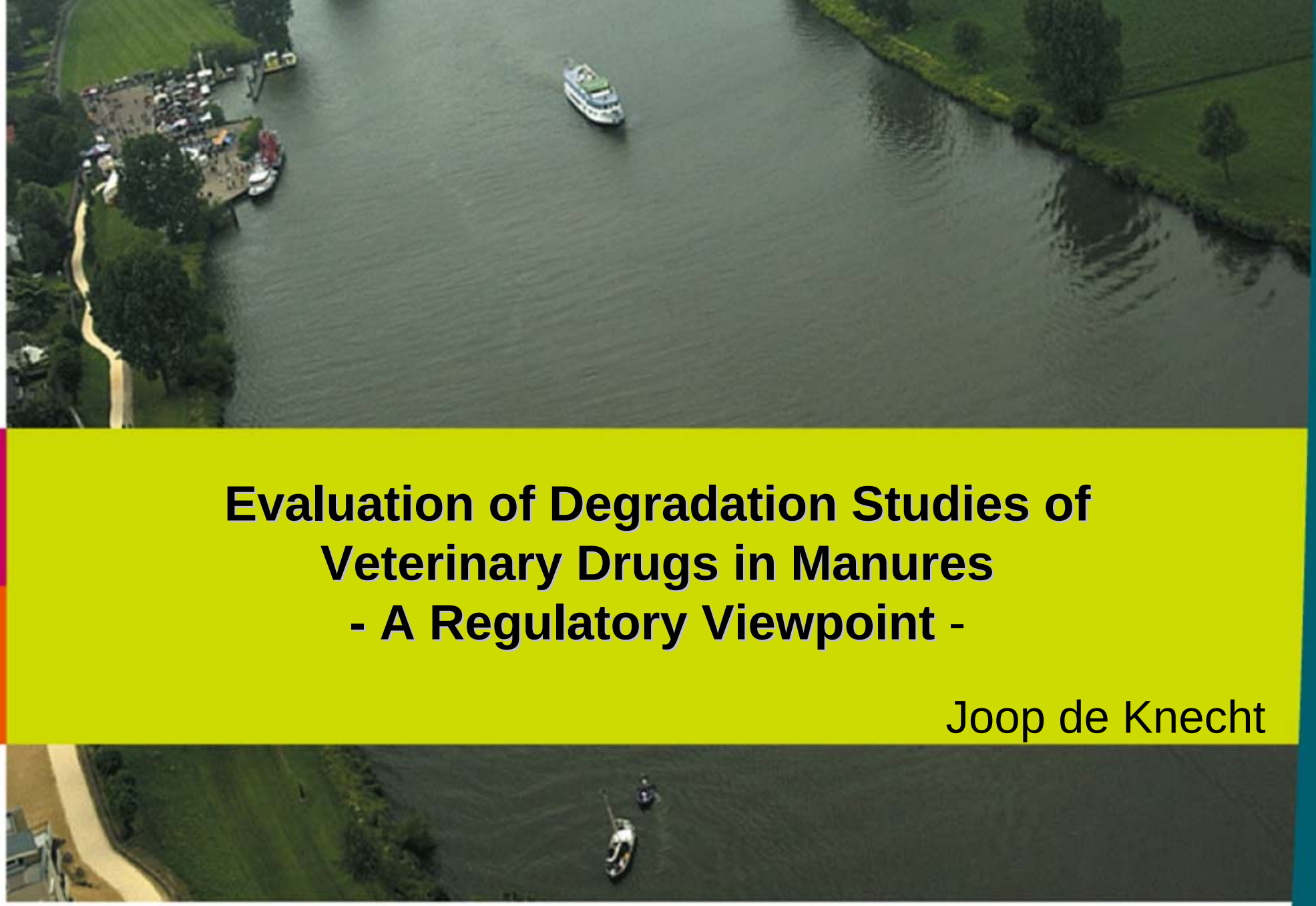

Evaluation of Degradation Studies of Veterinary Drugs in Manures
- A Regulatory Viewpoint -

Joop de Knecht

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Outline of the risk assessment

- Phase I
  Based on decision tree to identify VMPs of minor concern, given limited exposure;
  no fate & effects studies required

- Phase II
  Full risk assessment based on environmental fate and effect data (PEC versus PNEC) using a “tiered” approach

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Veterinary Medicinal Products likely to stop at Phase I

- Natural substances
- Companion animal products
- VMPS for which a relevant ERA/EIA already is available (minor species)
- VMPs to treat only individuals within groups
- VMPs which are extensively metabolized
- VMPs which totally mineralised in manure or when all degradation products representing 5% or less of the dose

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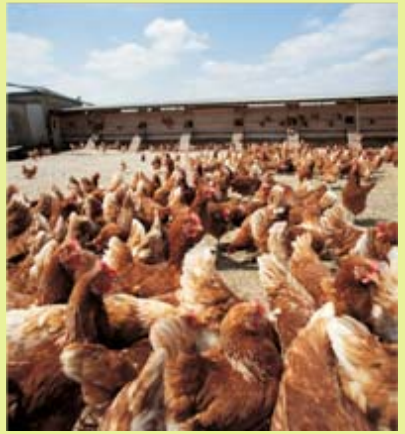
Risk assessment



Tier A data set

Derive PNEC using AF for Tier A
Estimate PEC (total residue) using “worst case” models

PEC/PNEC <1

NO!

Refine exposure

Yes!
STOP

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Refined exposure

Soil

- metabolism
- degradation – manure & soil

- using refined PEC
- FOCUS
- sediment partitioning

Surface water & sediment
Groundwater

Dung

- metabolism
- pattern of excretion

- metabolism
- sediment partitioning

Surface water & sediment

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Risk assessment

Tier A data set

Derive PNEC using AF for Tier A
Estimate PEC using “worst case” models

PEC/PNEC <1

NO!

Refine PEC based on metabolism and/or degradation and/or more realistic models

PEC/PNEC <1

Yes! STOP

NO!

Tier B chronic studies

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PEC Refinement based on degradation in manure

$$Mi = D \times Ad \times BW \times Fh$$

$$Mt = Mi \times e^{\left(\frac{\left(-\ln(2) \times \left(Tst / 2 \right)\right)}{DT_{50}} \right)}$$

$$PEC_{soil\ refined} = \left(\frac{Mt \times 170}{1500 \times 10000 \times 0.05 \times Ns} \right) \times 1000$$

Mi = Mass of active in manure
D = Daily dose of a.i.
Ad = No. days of treatment
BW = Animal body weight
Fh = Fraction of the herd treated
Tst = Length of time manure is stored
DT50 = Half-life of active in manure [days]
Mt = Mass of active in manure/slurry after the mean storage time

170 = EU nitrogen spreading limit
1500 = Bulk density of dry soil
10000 = Area of 1 hectare
0.05 = Depth of penetration into soil [m]
Ns = Nitrogen produced during storage time
1000 = Conversion factor

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Default storage times

Animal type	Number of animals raised per place per year	Storage time (days)
Calf / cattle / horse / fattening pig / poultry (excl. broiler)	≤ 3	91
Weaner pig and sow	6.9	53
Broiler	9	41
Duck	7	52

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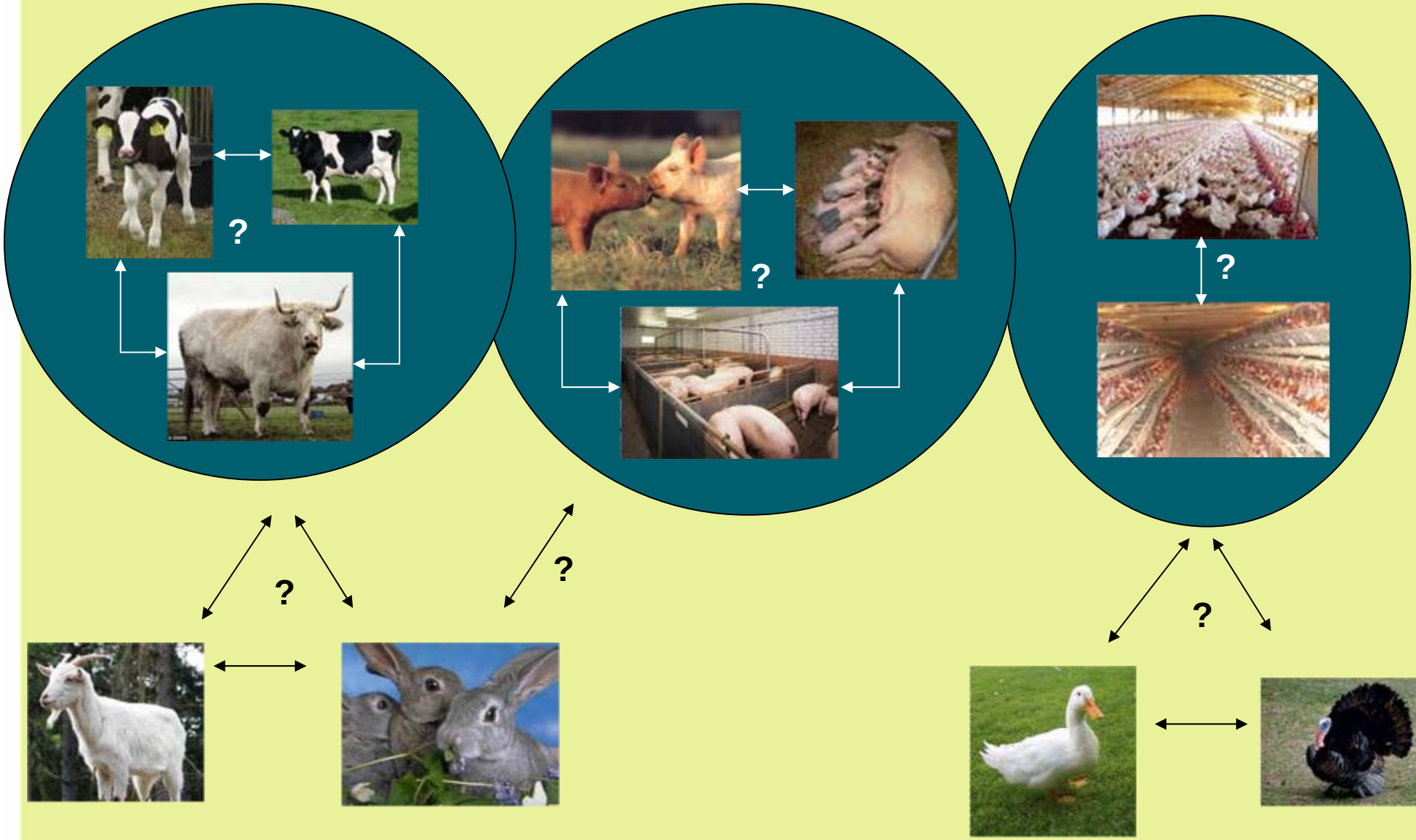
Issues related to the study design

- Selection and handling of the test manure
- Matrix characterisation of the manure
- Establishing test conditions
- Test substance and spiking procedure
- Extraction and determination of the test substance, metabolites and non extractable residues (eg, validation of analytical methods, setting criteria for recovery….)
- Data analysis (eg, kinetics)

Selection and handling of the test manure

- What should be the origin of manure?
- How do we store it?
- Can we define a reference manure
- Do we agree not to use tank manure to avoid contamination?
- Is it necessary to test more than one manure types from each target group?
- Can we extrapolate from one manure type to another?



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Should the degradation rate be determined in every manure type separately?

Matrix characterisation of the manure

- Proposed test parameters:
  - temperature
  - pH
  - (intestinal) microbial activity
  - organic matter
  - N and P content

Establishing test conditions

- Redox potential
  - Cattle and pigs on stables → Anaerobic
  - Poultry (rabbit, duck?) → Aerobic

  Can we define a threshold redox potential?
- Moisture content

  Poultry (including turkey ?) → dry (50%)
  Cattle and pigs on stables → wet
  rabbit, turkey, duck → dry (%?)
- Test duration

  100 days
- Sterile control needed to make distinction between biotic and abiotic degradation
- Test temperature at relevant storage temperatures (pig: 20°C; cattle: 10°C; chickens / horse 25°C)

radiolabelled versus non-radiolabelled material

Radiolabelled material preferred because:

- mass balance is easier to achieve
- facilitates the interpretation of test results (recovery, transformation, fraction of bound residue)
- mineralization easier detected
- possibly improve the detection limits

radiolabelled versus non-radiolabelled material

Experiences with studies performed with non-radiolabelled substances

- mass balance can be achieved with easy extractable substances in which the degradation of parent compound can be linked to formation of metabolite(s)
- when no metabolites / CO_2 are measured, often no distinction can be made between degradation and adsorption (formation of bound residues)

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Extraction method

- Recovery should be:
  90 – 110 % for labelled chemicals
  70 – 110 % for non-labelled chemicals

- method should allow extraction of polar and non-polar compounds

- The extraction should be as severe as possible without disruption of the parent compounds and its metabolites. Bound residue will be considered to be parent compound

- Methane production is difficult to measure.
  Alternatively the reaction equation (Buswell) can be used

Example extraction method

- Step 1: acetonitrile without and with hydrochloric acid
- Step 2: concentrated HCl

	MET 1	MET 2	MET 3
Extraction Step 1	4.4	2.4	9.9
Extraction Step 2	7.2	13.2	1.0
Totaal	11.7	15.3	10.9

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Data analysis

- How should we deal with non first-order dissipation interpretation?
- How should the formation of non-extractable residues (NER) be considered in determining the degradation rate?
- Should we set a maximum percentage NER to reject to disregard the result of the study?

Metabolites

According to VICH guideline all metabolites ≥ 10% not part of biochemical pathways should be considered.

Main questions:

- How relevant are metabolites?
- How to continue the risk assessment when parent compound completely degrades

Does a pharmaceutical inactivation also results in a reduced potential harmful effect in the environment?

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