Environmental Risk Assessment
Part of the overall Risk / Benefit Assessment
of veterinary medicinal products

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List of abbreviations / Glossary

AF	Assessment Factor
CVMP	Committee for Medicinal Products Veterinary Use
Dir.	Directive
DTx	Time to degradation of x % of original concentration of the compound in the tested soil
ERA	Environmental Risk Assessment
EC	European Commission
ECx	Concentration of a test substance which results in x % of the test animal being adversely effected
EMEA	European Medicines Agency
EU	European Union
LCx	Concentration of a test substance which results in a x % mortality of the test species
LOEC	Lowest Observed Effect Concentration
NOEL	No Observed Effect Concentration
NSAID	Non-Steroidal Anti-Inflammatory Drug
OECD	Organization for Economic Co-operation and Development
PEC	Predicted Environmental Concentration
PNEC	Predicted No Effect Concentration
Reg.	Regulative
RQ	Risk Quotient
SPC	Summary of Product Characteristics
VMP	Veterinary Medicinal Product
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

1. Introduction and legal frame

Whereas fate and possible impact on the environment of domestic and industrial chemicals have been addressed by European legislation already for decades, similar regulations considering VMPs have only been initiated by the European Commission when Dir. 92/18/EEC was issued to amend Dir. 81/852/EEC (1).

Dir. 81/852/EEC (2) has to be seen as the basic step towards a harmonised European approach regarding data requirements for VMPs to ensuring a high level of quality, safety and efficacy. However, in its safety section the directive focus on the actives pharmacological and toxicological potential to humans and mammals. Only when amended by Dir. 92/18/EEC (1) basic obligations for an Environmental Risk Assessment (ERA) were introduced. It was stated that „the purpose of the study of the ecotoxicity of a veterinary medicinal product is to assess the potential harmful effects which the use of the product may cause to the environment and to identify any precautionary measures which may be necessary to reduce such risks“. This directive outlined basic requirements for conducting an ERA in a two-phase approach, which became mandatory to all applications for marketing authorisation other than so called abridged applications. The first phase of such an assessment aims to reveal VMPs with a high potential of exposure of the environment to the product, its ingredient or relevant metabolites, while in a second phase such products should be subject of investigations regarding their effects on particular ecosystems. A guidance document on the assessment of the potential exposure of the environment to a VMP was issued by the CVMP in 1997 (3).

When Dir. 81/852/EEC was repealed by Dir. 2001/82/EC (4) abridged applications remained to be exempted from an ERA. However, recent amendment of the latter by Dir. 2004/28/EC introduced a much stricter approach to protect environment from possible negative effects of VMPs. An ERA became mandatory for all new applications, independent of the application procedure and type („full“, „generic“ etc.) and is therefore required for all marketing authorisation applications submitted in the EU irrespective of the underlying legal basis (5).

Moreover Dir. 2004/28/EC (6) has introduced the risk/benefit balance as the crucial parameter for granting a marketing authorisation. Different to human legislation possible risks of a VMP to the environment have to be comprised in its overall risk potential and may lead to a negative decision concerning granting of a marketing authorisation.

Art. 30 of Dir. 2001/82/EC as amended reads: “The authorisation shall also be refused if…it is clear that: (a) the risk-benefit balance of the veterinary medicinal product is, under the authorised conditions of use, unfavourable…”. The risk of a VMP has been defined in Art. 1 as any risk relating to the quality, safety and efficacy of the VMP, with regards to animal or human health and any risk of undesirable effects to the environment.

Reg. EC/726/2004/ (7) follows the same approach as it states that the ecotoxical potential of a VMP must be considered when a central marketing application is assessed. Moreover, both central and national authorisations may be renewed after five years on the basis of a re-evaluation of the risk-benefit balance (7, 8) considering the possible risks to the environment.

In order to enable any applicant of a marketing authorisation to meet the current legal requirements, three detailed CVMP guidelines have been published. The „Guideline on Environmental Impact Assessment for VMPs– Phase I“ (9) and „Guideline on Environmental Impact Assessment for VMPs– Phase II“ (10) are each the results of a VICH process and reflect the common requirements of the three VICH regions. In addition the „Guideline on Environmental Impact Assessment for VMPs in Support of the VICH Guidelines GL 6 and GL 36“ (5),initiated by the EMEA, intents to amend the VICH guidelines by specific technical guidance in areas where the VICH guidelines are more general or refer to further regional guidance.

2. Issues under Examination

2.1. Environmental Risk Assessment

Dir. 2001/82/EC as amended (11) requires an assessment of the risk of the VMP to the environment that is meant to be conducted in two phases. In the Phase I the extent of environmental exposure should be estimated based on the intended use of the VMP. It is assumed that VMPs with limited use and limited environmental exposure will have limited environmental effects and thus stop in Phase I. Furthermore Phase I also aims to identify VMPs that require a more extensive assessment during a second phase. Thus in Phase II the fate and the effects of the active on non target species and ecosystems are to be assessed.

As a whole, the risk assessment is structured around the risk quotient. The risk quotient is defined as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC).The risk quotient is assumed to indicate the likelihood of adverse effects occurring.

2.1.1. Phase I Assessment

The „Guideline on Environmental Impact Assessment for VMPs– Phase I“ (9) in conjunction with more specific „Guideline on Environmental Impact Assessment for VMPs in Support of the VICH Guidelines GL 6 and GL 36“ (5) provide a straight forward decision tree (Figure 1).

The investigator should assess the potential extent of exposure of the environment to the product by a number of questions. In many cases the question will identify those products, that are not expected to have a high ecotoxical potential and for which the assessment will stop in Phase I. For the assessment the applicant should take the target species, the method of administration, the pattern of use, and the characteristics of the constituents of the VMP into account.

In Phase I a total residue approach will normally be assumed. Where the VMP under investigation does not meet any of the exclusion criteria it will automatically move to a Phase II assessment.

Question 1 to Question 4 excludes all products from Phase II:

- that are not considered as a VMP in the relevant VICH region or member state
- that is a natural substance and its use would not alter the concentration or distribution in the environment
- that are intended to be used in non-food animals only
- that are intended for use in a minor species when an ERA for a similar reared and treated major species already exists

Question 5 excludes those VMPs that are to be used only in a small numbers of animals in a flock or a herd. According to European guidance (5) this applies merely for:

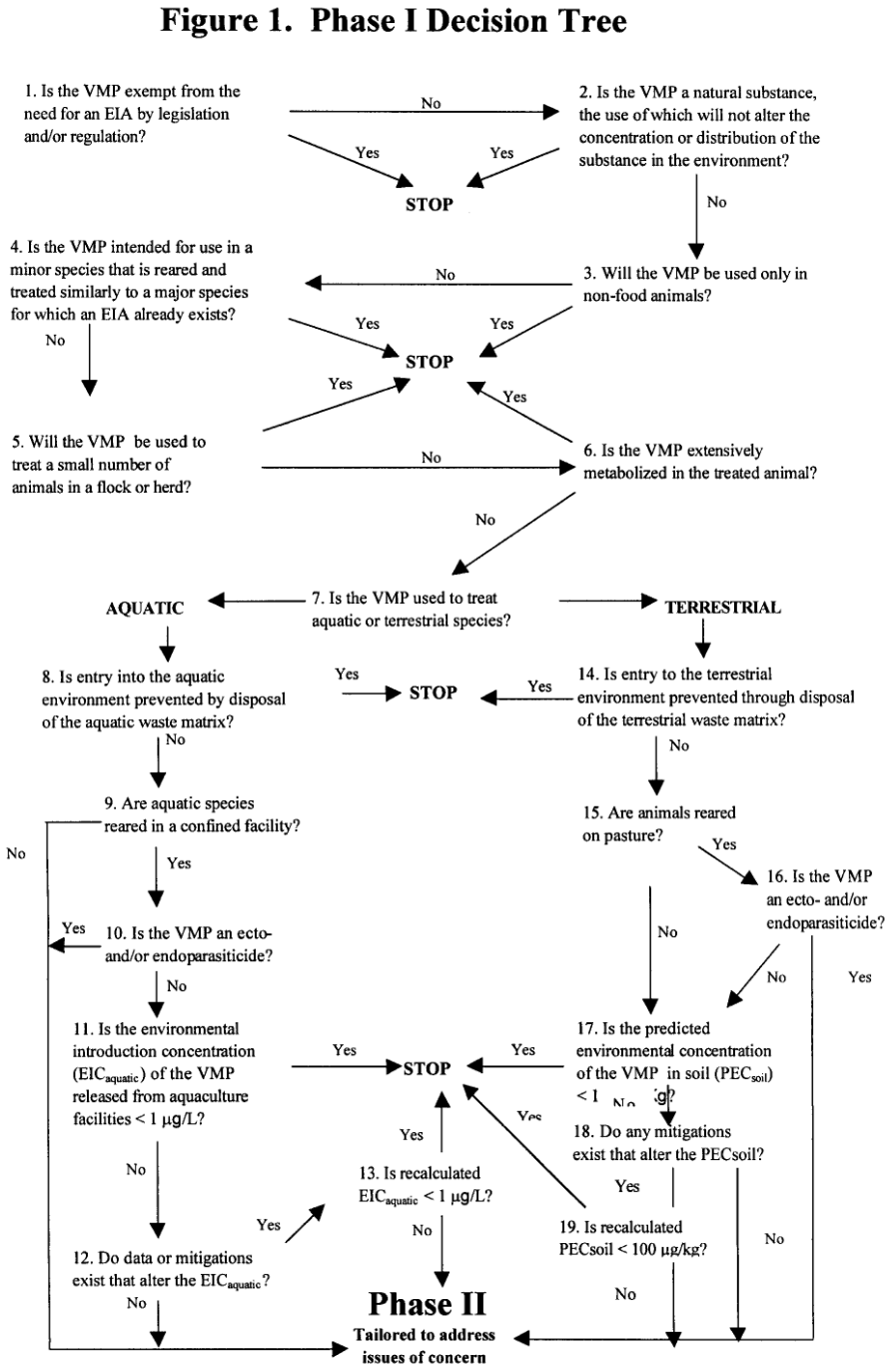
- Anaesthetics and sedatives
- Injectable antibiotics (except all those used in pigs, all those used to treat respiratory disease in cattle or foot rot in sheep)
- Injectable corticosteroids
- Hormones (except those which have a zootechnical use)
- Injectable NSAIDs

A VMP that can be proven to be extensively metabolised (e. g. by results of residue depletion studies) would not need to undergo Phase II (Question 6). Therefore, evidence has to be brought that the metabolites have lost structural resemblance with the parent drug, are common to basic biochemical pathways or that no single metabolite or the parent drug exceeds 5 % of the total.

VMPs intended for use in the aquatic branch will be addressed differently by the guidance documents to those intended for the terrestrial branch (Question 7). As the

authors considers the terrestrial branch to be by far the more important one it will be presented here more detailed than the aquatic branch.

Figure 1: Decision tree Phase I



Terrestrial branch

VMPs that will not entry the environment on any occasion due to disposal of the waste matrix (e. g. incineration) will not need further assessment (Question 14), while ecto- and endoparasiticide used in pasture animals have to undergo Phase II assessment in any case (Question 15-16).

For those VMPs that could not be excluded nor for which a Phase II assessment has been identified as mandatory the investigator is now asked to estimate the predicted environmental concentration of the VMP in soil (PEC_{soil}). The EMEA guidance (5) provides the equation presented in Figure 2 for intensively reared animals, that are presumed to be housed indoors throughout the production cycle and the active residue is excreted in the manure:

Figure 2: Equation for estimation of PEC_{soil} for intensively reared livestock

$$PEC_{soil} = \left(\frac{D \times Ad \times BW \times P \times 170 \times Fh}{1500 \times 10000 \times 0.05 \times Ny \times H} \right) \times 1000$$

where:

PEC_{soil}	=	Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$]
D	=	Daily Dose of the active ingredient [$mg.kg_{bw}^{-1}.d^{-1}$]
Ad	=	Number of days of treatment [d]
BW	=	Animal body weight [kg_{bw}] (see Table 3.)
P	=	Animal turnover rate per place per year (see Table 3.) [$place^{-1}.y^{-1}$]
170	=	EU Nitrogen spreading limit [$kg\ N.ha^{-1}$]
Fh	=	Fraction of herd treated [value between 0 and 1] (see Table 2.)
1500	=	Bulk Density of dry soil [$kg.m^{-3}$]
10000	=	Area of 1 hectare [$m^2.ha^{-1}$]
0.05	=	Depth of penetration into soil [m]
Ny	=	Nitrogen produced in one year per place [$kg.N.\ place^{-1}.y^{-1}$] (see Table 3.)
H	=	Housing factor either 1 for animals housed throughout the year or 0.5 for animals housed for only 6 months (see Table 3.)
1000	=	conversion factor [1000 $\mu g.mg^{-1}$]

In this worst case approach it is assumed that 100 % of the dose applied will be excreted by the animal and thus entry the environment. At this stage no data on metabolism or degradation in the manure will be taken into account.

The equation aims to estimate the amount of the VMP each kilogram soil will be contaminated with per year. Thus D x Ad x BW expresses the average amount of the

VMP which will be used for a treatment of a single individual, while Fh considers the average fraction of the herd that will be treated per production cycle.

It is presumed that any group of animals will at least be affected once by the condition the VMP is intended for. This is reflected by introducing P to the equation. So far D x Ad x BW x Fh x P expresses the average amount of the VMP that is used in a given situation per place per year.

This amount consequentially will entry the manure and concentration in the manure can be expressed by considering the amount of manure that is produced by the investigated type of animal per year and place. As common for agriculture sciences this is expressed as nitrogen, since this is a fairly constant parameter.

Consequently (D x Ad x BW x Fh x P) / Ny expresses the amount of the VMP in the manure per kg nitrogen. In European agriculture 170 kg nitrogen per hectare per year is the maximum permitted for manuring. By considering this factor the maximum amount of the VMP that is spread on a hectare per year is estimated. This is believed to be distributed equally in the top 5 cm of the soil, which is equal to 1500 x 10.000 x 0.05 or 750.000 kg soil. Thus the calculation results in the predicted environmental concentration of the VMP in a kilogram soil per year.

While some factors of the PEC equation are constant others depend on the condition the VMP will be used for. In a very general approach veterinarian surgeons have been interviewed on the fraction of herds that are treated when a VMP of a specific pharmaceutical class is indicated. Results, which should be used as standard values, are published in the EMEA technical guidance (5) (see Figure 3).

Figure 3: Fraction of the herd - Standard values published in the EMEA guidance (5)

Product group	% herd treatment
Anthelmintics	100
Products for treatment of diarrhoea in calves, lambs and pigs (excluding products administered in feed and water)	30
Coccidiostatics	100
Ectoparasiticides	100
Intramammary preparations:	
for drying off	100
in lactating animals	25
Antibiotics (feed and water medication)	100
Antibiotics (injectable)	
all pig treatments	50
respiratory infections in cattle	50
foot rot in sheep	100
Teat dip and sprays	100
All products for poultry	100
All products for fish	100

*The % herd treatments in the table were compiled after discussion with veterinary surgeons in a number of EU Member States

For PEC_{soil} calculation the applicant has to consult the Summary of Product Characteristics (SPC) of the VMP under investigation and consider the standard value.

Moreover the guideline introduces average values for the number of animals raised per place per year, bodyweight, nitrogen production and housing factors. Data rely on publications of Montforts (12), Smith and Frost (13) and Smith (14).

The same principle applies for equation for the predicted environmental concentration of VMPs used in pasture animals or as teat dips. For details the reader is advised to refer to the Guideline (5).

In most cases a VMP will be used in more than one target species or age cohort and in many cases even for more than one condition. However, PEC_{soil} estimation will be obligatory for each of the claimed indication. In cases where the PEC_{soil} value is found to be lower than 100 µg/kg soil, the assessment may stop and no further evaluation is needed. Nevertheless assessment has to continue whenever the value is beyond that limit. The trigger value of 100 µg/kg has been agreed upon as it has been shown in a review of ecotoxical data to be below the level having effects on earthworms, microbes and plants (15).

Having calculated the PEC(s) the investigator might realises that chemical characteristics of the active substance which are likely to result in a high susceptibility for degradation in manure have not yet been considered. Question 17 of the decision tree offers the possibility to alter the PEC_{soil} by providing data that suggest a rapid and full degradation of the active molecule. Criteria that would allow to end the assessment at this point are identical to those of extensive metabolism as referred to in question 6 (degradation products all representing less than 5 % or less of the dose).

Up-to-date there is no established study protocol available for degradation testing in manure. The EMEA guideline merely provides the frame for a degradation study. It recommends to utilize radiolabelled test compounds, manure of (each) target species and to consider certain study temperatures, moistness and oxygen conditions depended on the test manure. If no degradation can be shown in 30 days no alteration of the PEC_{soil} can be stressed.

Both relevant guidelines (5, 9) are not consistent whether the applicant is allowed to recalculate the PEC_{soil} if he demonstrates that a mitigation exists. While the VICH guidance suggests the latter (9) the EMEA paper excludes this possibility but refers to criteria of complete metabolism or degradation (5). However, the EMEA guideline will be binding for applications in the EU.

At the end of the Phase I assessment the investigator either has found the VMP under examination may be excluded from any further assessment or that the predicted environmental concentration will be above the trigger of 100 µg/kg and thus a Phase II assessment is mandatory.

Aquatic Branch

Assessment of VMPs used in the aquatic branch follows the same principal as for the terrestrial branch. VMPs used in those cases where the entry into the environment is prevented by disposal measures may stop in Phase I (Question 8), whereas those that are used in aquaculture facilities that are contiguous with the aquatic environment (Question 9) or are ecto- or endoparasiticides (Question 10) will proceed directly to Phase II. Environmental introduction concentration ($EIC_{aquatic}$) is much easier to estimate, as it will be equal to the recommended dose per litre. The trigger value for the $EIC_{aquatic}$ is 1 µg/L.

2.1.2. Phase II Assessment

While assessment in Phase I is much more general, Phase II relies on the generation of specific data on the environmental fate and the effects to the different ecological compartments.

Directive 2001/82/EC reads:

"in the second phase, having regard to the extent of exposure of the product to the environment, and the available information about the physical/chemical, pharmacological and/or toxicological properties of the compound which has been obtained during the conduct of the other tests and trials required by this Directive, the investigator shall then consider whether further specific investigation of the effects of the product on particular eco-systems is necessary".

The regulatory guidances (5, 10) use a two-tiered approach to the ERA. The first tier, Tier A, makes use of simpler, less expensive studies to produce a conservative assessment of the risk based on exposure and effects in the environmental

compartment of concern. If the assessment cannot be completed with such data, due to a prediction of unacceptable risk, then the applicant progresses to Tier B to refine the EIA (5).

The principal of the Phase II assessment is based on a risk quotient (RQ) approach. The RQ is determined by the ratio of the PEC (defined as the concentration of the parent compound and metabolites predicted to be present in soil, water and sediment compartment) and the PNEC on non target organism (determined from the experimentally determined toxicological effects). The RQ is compared against a value of one and a value less than one indicates that no further testing is recommended.

To ensure high quality data regulatory guidances suggest utilising on high level standardized study protocols.

There is guidance available for all three branches, namely the aquaculture branch, the intensively reared animals' branch and the pasture animals' branch. For middle Europe the most important branch will be the intensively reared animal branch. Thus the idea of the Phase II assessment will be examined on the example of the latter. For more details on the other branches the reader is referred to the guidance documents (5, 10).

2.1.2.1. Tier A

At the beginning of Phase II, and in order to be able to define a PNEC, a Tier A base data set on the fate and effects of the VMP is produced by the applicant. This data set is a key element of the assessment procedure allowing for the rapid identification of hazards and risks associated with the use of the product (5). To ensure high quality of data the applicant is advised to stick to the recommended study protocols of the European Commission and OECD and to apply the principles of Good Laboratory Practices.

Recommended studies include investigation on the physical-chemical properties, on the environmental fate and the environmental effects.

Tier A - Physical-Chemical Properties Studies

The studies shown in Table 1 are recommended to conclude on the active substance behaviour in the environment. OECD study protocols are available for any of these studies.

Table 1: Study protocols to determine VMPs physical-chemical properties

STUDY	GUIDELINE
Water Solubility	OECD 105
Dissociation Constants in Water	OECD 112
UV-Visible Absorption Spectrum	OECD 101
Melting Point/ Melting Range	OECD 102
Vapour Pressure	OECD 104
n-Octanol/Water Partition Coefficient	OECD 107 or 117

Tier A - Environmental Fate Studies

A set of studies should be performed in order to learn about the fate of the active substance in the environment.

Soil Adsorption/Desorption (as summarised in the OECD abstract (16)**)**

This Test Guideline is aimed at estimating the adsorption/desorption behaviour of a chemical on different soil types. The goal is to obtain a sorption value which can be used to predict partitioning under a variety of environmental conditions; to this end, equilibrium adsorption coefficients for a chemical on various soils are determined as a function of soil characteristics (organic carbon, clay content, soil texture, and pH). The test comprises three tiers. The tier 1 is the preliminary study, the tier 2 is the screening test (in 5 soils) and the tier 3 is the determination of Freundlich adsorption isotherms or

the study of desorption by means of desorption kinetics/Freundlich desorption isotherms, as appropriate. Two methods are possible for analyse: the indirect method and the direct method. The indirect method consists of the adjunction of the test substance to soil samples, the agitation of the mixture for an appropriate time, the analysis of the aqueous phase after centrifugation and the filtration of the soil suspension. The amount of test substance adsorbed on the soil sample is calculated as the difference between the amount of test substance initially present in solution and the amount remaining at the end of the experiment. The direct method is recommended when the difference in the solution concentration of the substance cannot be accurately determined.

Soil Biodegradation (as summarised in the OECD abstract (17))

The method described in this Test Guideline is designed for evaluating aerobic and anaerobic transformation of chemicals in soil. The experiments are performed to determine the rate of transformation of the test substance, and the nature and rates of formation and decline of transformation products, to which plants and soil organisms may be exposed.

About 50 to 200 g soil samples (a sandy loam or silty loam or loam or loamy sand) are treated with the test substance and incubated in the dark, in biometer-type flasks or in flow-through systems under controlled laboratory conditions. The treatment rate should correspond to the highest application rate of a crop protection product recommended in the use instructions. Also untreated soil samples are incubated under test conditions. These samples are used for biomass measurements during and at the end of the studies. The rate and pathway studies should normally not exceed 120 days. Duplicate incubation flasks are removed at appropriate time intervals and the soil samples extracted with appropriate solvents, of different polarity, and analysed for the test substance and/or transformation products. Volatile products are also collected for analysis using appropriate adsorption devices. Using 14C-labelled material, the various mineralization rates of the test substance can be measured by trapping evolved

14CO2 and a mass balance, including the formation of soil bound residues, can be established.

Degradation in aquatic systems (as summarised in the OECD abstract (18))

This Test Guideline describes a laboratory test method to assess aerobic and anaerobic transformation of organic chemicals in aquatic sediment systems. The method permits the measurement of (i) the transformation rate of the test substance in a water-sediment system and in the sediment (ii) the mineralization rate of the test substance and/or its transformation products, (iii) the distribution of the test substance and its transformation products between the two phases during a period of incubation in the dark, at constant temperature, and (iv) the identification and quantification of transformation products in water and sediment phases including mass balance.

At least two sediments different with respect to organic carbon content and texture are used. Ideally the test substance (one concentration) should be applied as an aqueous solution into the water phase. The duration of the experiment should normally not exceed 100 days, and should continue until the degradation pathway and water/sediment distribution pattern are established or when 90 % of the test substance has been removed by transformation and/or volatilisation. The number of sampling times should be at least six. The study includes: concentration in the water and sediment of the test substance and the transformation products at every sampling time; results from gases/volatiles trapping systems at each sampling time; mineralization rates; and non-extractable residues in sediment at each sampling point. Half-lives, DT50, DT75 and DT90 values are determined where the data warrant.

Photolysis

This study may be performed optional as it is presumed that there will be little exposure of the active to light in soil or manure, while photolysis might play a role for VMPs that are added directly to the water. However, no guideline or recommended study protocol is available and thus regulatory guidance might be sought.

Hydrolysis

Optional and according to OECD 111 (19).

Tier A – Effects Testing

A set of toxicological tests on non-target species is recommended in order to estimate the PNEC as it will be considered for the RQ. The PNEC has to be determined from the defined effect endpoint divided by an appropriate assessment factor (AF).This factor intends to cover uncertainties, e. g. intra- and inter-laboratory or species depending variations. The AF value as it is recommended in the guidance (10) varies between the type of study. For a summary of toxicological endpoints and applied AF see Table 2.

For VMPs to be used in intensively reared animals an indirect entry of the active into the aquatic systems is expected. At least one species should be tested from each of the three taxonomic levels, e. g. algae, invertebrates and fish (10). Moreover, to access possible effects on terrestrial compartments variations on nitrogen transformation activity of soil microorganisms, toxicity towards terrestrial plants and earthworms are expected to be examined. In the case of endo- or ectoparasiticides used in pasture animals additional toxicity studies on dung fly larvae and dung beetle larvae are recommended.

Table 2: Toxicity endpoints and assessment factors (AF) of obligatory Tier A toxicity test on non-target species

Study	Toxicity endpoint	AF
Algae growth inhibition (20)	EC50	100
Daphina immobilization (21)	EC50	1000
Fish acute toxicity (22)	LC50	1000
Nitrogen Transformation (28 days) (23)	≤ 25 % of control	Not relevant
Terrestrial plants (24)	EC50	100
Earthworm Subacute / reproduction (25)	NOEC	10

Algae growth inhibition (as summarised in the OECD abstract (20))

The purpose of this test is to determine the effects of a substance on the growth of freshwater microalgae and/or cyanobacteria. Exponentially growing test organisms are exposed to the test substance in batch cultures over a period of normally 72 hours. The system response is the reduction of growth in a series of algal cultures exposed to, at least, five concentrations of a test substance. Three replicates at each test concentration should be used. The response is evaluated as a function of the exposure concentration in comparison with the average growth of control cultures. The cultures are allowed unrestricted exponential growth under nutrient sufficient conditions (two alternative growth media: the OECD and the AAP) and continuous fluorescent illumination. Growth and growth inhibition are quantified from measurements of the algal biomass as a function of time. The limit test corresponds to one dose level of 100 mg/L. This study includes: the determination, at least daily, of the algal biomass; the measure of the pH (at the beginning and at the end); microscopic observation. This

Test Guideline describes two response variables: average specific growth rate, and yield.

Daphnia immobilization (as summarised in the OECD abstract (21))

This Test Guideline describes an acute toxicity test to assess effects of chemicals towards daphnids (usually Daphnia magna Staus). Young daphnids, aged less than 24 hours at the start of the test, are exposed to the test substance at a range of concentrations (at least five concentrations) for a period of 48 hours. Immobilisation is recorded at 24 hours and 48 hours and compared with control values. The results are analysed in order to calculate the EC50 at 48h. Determination of the EC50 at 24h is optional. At least 20 animals, preferably divided into four groups of five animals each, should be used at each test concentration and for the controls. At least 2 ml of test solution should be provided for each animal (i.e. a volume of 10 ml for five daphnids per test vessel). The limit test corresponds to one dose level of 100 mg/L. The study report should include the observation for immobilized daphnids at 24 and 48 hours after the beginning of the test and the measures of dissolved oxygen, pH, concentration of the test substance, at the beginning and end of the test.

Fish acute toxicity (as summarised in the OECD abstract (22))

The fish are exposed to the test substance preferably for a period of 96 hours. Mortalities are recorded at 24, 48, 72 and 96 hours and the concentrations which kill 50 per cent of the fish (LC50) are determined where possible. One or more species may be used, the choice being at the discretion of the testing laboratory. At least seven fishes must be used at each test concentration and in the controls. The test substance should be administered to, at least, five concentrations in a geometric series with a factor preferably not exceeding 2.2. The limit test corresponds to one dose level of 100 mg/L. This study includes the observations of fish at least after 24, 48, 72 and 96 hours. The cumulative percentage mortality for each exposure period is plotted against concentration on logarithmic probability paper.

Nitrogen Transformation (as summarised in the OECD abstract (23))

This Test Guideline describes a laboratory test method designed to investigate the long-term effects of chemicals, after a single exposure, on nitrogen transformation activity of soil microorganisms. Sieved soil is amended with powdered plant meal and either treated with the test substance or left untreated. For agrochemicals, a minimum of two test concentrations are recommended (five for non agrochemicals) and these should be chosen in relation to the highest concentration anticipated in the field. The soil is divided into three portions of equal weight (six for non agrochemicals). Two portions are mixed with the carrier containing the product (five for non agrochemicals), and the other is mixed with the carrier without the product (control). A minimum of three replicates for both treated and untreated soils is recommended. After 0, 7, 14 days and 28 days of incubation, samples of treated and control soils are extracted with an appropriate solvent, and the quantities of nitrate in the extracts are determined. All tests run for at least 28 days. If, on the 28th day, differences between treated and untreated soils are equal to or greater than 25%, measurements are continued to a maximum of 100 days. Results from tests with multiple concentrations are analysed using a regression model, and the ECx values are calculated.

Terrestrial Plant Test (as summarised in the OECD abstract (24))

This Test Guideline is designed to assess effects on seedling emergence and early growth of higher plants following exposure to the test substance applied to the soil surface or into the soil. Seeds are placed in contact with soil treated with the test substance and evaluated for effects following usually 14 to 21 days after 50 % emergence of the seedlings in the control group. Endpoints measured are visual assessment of seedling emergence, biomass measurements, shoot height, and the visible detrimental effects on different parts of the plant. The test can be conducted in order to determine the dose-response curve, or at a single concentration/rate as a limit test, according to the aim of the study. An appropriate statistical analysis is used to obtain effective concentration ECx or effective application rate ERx for the most sensitive parameter(s) of interest. Also, the no observed effect concentration (NOEC) and lowest observed effect concentration (LOEC) can be calculated in this test.

Earthworm Reproduction Test (as summarised in the OECD abstract (25))

This Test Guideline is designed to be used for assessing the effects of chemicals in soil on the reproductive output (and other sub-lethal end points) of the earthworm species Eisenia fetida or Eisenia andrei. Adult worms are exposed to a range of concentrations of the test substance either mixed into the soil or applied to the soil surface. The range of test concentrations is selected to encompass those likely to cause both sub-lethal and lethal effects over a period of eight weeks. The limit test corresponds to one dose level of 1000 mg/kg. This study includes the observation of unusual behaviour and morphology, the counting and weighing of the adult worms after the four primary weeks, the number of juveniles hatched at the end of the second 4-week period. The reproductive output of the worms exposed to the test substance is compared to that of the control(s) in order to determine the no observed effect concentration (NOEC) and/or ECx by using a regression model to estimate the concentration that would cause an x % reduction in reproductive output. The test concentrations should bracket the ECx so that the ECx then comes from interpolation rather than extrapolation.

Tier A - PEC refinement

In order to estimate the RQ the $PEC_{initial}$ is calculated based on a total residue approach. As in Phase I no data on metabolism/excretion or degradation are considered. The RQ at this stage will be performed by comparing the $PEC_{initial}$ to the determined PNEC for each of the taxonomic levels tested. If the RQs are <1 for all taxonomic levels no further assessment is recommended. In cases the RQ exceeds the value of one refinement of the $PEC_{initial}$ by considering data on metabolism or degradation should be performed.

Refinement based on metabolism

Data generated during metabolism studies should be considered in order to estimate the actual active residues that entry the environment. The VICH Phase II guidance (10) suggest that this should be the sum of the parent active compound and all metabolites that represent more than 10 % of the administered dose and which do not form part of biochemical pathways.

Refinement based on degradation in manure

If degradation in the manure is to be considered, data should always be generated under realistic worst-case storage conditions. Studies on the issue are not included in the recommended Tier A studies. However, in some case relevant studies have already been performed during Phase I. If not conditions for such studies should be set according to what has been described for the Phase I assessment. As a result the applicant should be able to present a half-life value for the active in manure. EMEA guidance (5) suggests an equation by which the refined PEC might be calculated considering degradation during standard storage periods.

Refinement based on degradation in soil

According to the EMEA guidance (5) refinement based on soil degradation data is only possible when it is realistic to assume that manure is spread in more than one spreading event. Is that the case the concentration calculated after the last spreading event should be considered, as this is the point when maximum concentration throughout the year cycle will be reached.

The $PEC_{refined}$ will again be considered for recalculation of the RQs for the concerned taxonomic levels. If this results in RQs < 1 for all levels no further assessment will be necessary. For taxonomic levels where the RQ still exceeds this value a Tier B assessment is triggered.

Attention should be paid to the fact that for the intensively reared animal branch a solely consideration of the PEC_{soil} will not be satisfactory. As VMPs used in that branch are assumed to entry the aquatic environment, too, RQs comparing the PEC_{water} with the PNEC have to be calculated additionally. For details refer to the guidances (5, 10). However the basic principle applies for any compartment.

2.1.2.2. Tier B

Triggers for further testing in Tier B are RQs exceeding the value of 1, even when considering a refined PEC or in the case of nitrogen transformation an effect > 25%. Only the affected taxonomic levels need to undergo a further Tier B testing. Nevertheless, whenever there is evidence that bioaccumulation might be possible, e. g. high concentrations of the active in fat, a bioconcentration factor study is recommended. As this is a complex issue which will not affect most of the VMPs, it should only be mentioned here, as there is comprehensive guidance in the guidelines (5, 10). The same applies to conduction of specific environmental effect studies, which are recommended when there is evidence on sediment invertebrate toxicity.

As a rule Tier B assessment bases on more advanced environmental effects studies utilising the same taxonomic species but applying different toxicological endpoints and lower assessment factor. Details on relevant studies for intensively reared animal branch are given in Table 3.

Table 3: Toxicity endpoints and assessment factors (AF) of obligatory Tier B toxicity test on non-target species

Study	Toxicity endpoint (Tier A)	AF (Tier A)
Algae growth inhibition (20)	NOEC (EC50)	10 (100)
Daphina magna reproduction (26)	NOEC (EC50)	10 (1000)
Fish acute toxicity (27)	NOEC (None)	10 (None)
Nitrogen Transformation (100 days) (23)	≤ 25 % of control (28 days)	Not relevant
Terrestrial plants growths, more species (24)	NOEC (EC50)	10 (100)

Results of these additional tests will be used for some further RQ. If after the Tier B testing the RQ is ≥ 1 or in case of soil micro-organism an effect > 25% the guidances recommend to seek regulatory advice (5, 10).

3. Conclusion

3.1. Conclusions for different classes of VMPs

The above presented approach of the European Union and the additional members of the VICH region to evaluation of environmental risks caused by VMPs will result in very different consequences for the VMPs.

Specific requirements for the individual ERA are determined by the characteristics of the VMP as they are outlined in the SPC. Complexity of the ERA will depend on the nature of the chemical compound, the claimed target species, pharmaceutical class, indications and dosage regime. Consequentially it is possible to distinguish groups of VMPs affected differently by the current legislative.

Industry should be aware that current requirements will not only account for new marketing application, but that it is political intention to comprise all active substances that are currently on the market. For a more specific approach for generic applications, renewals and variation applications there is a further CVMP guidance document expected to be published soon (28).

3.1.1. VMPs for which a PEC calculation is not mandatory

Phase I decision tree will identify a great number of VMPs for which Phase I assessment can be completed without PEC estimation.

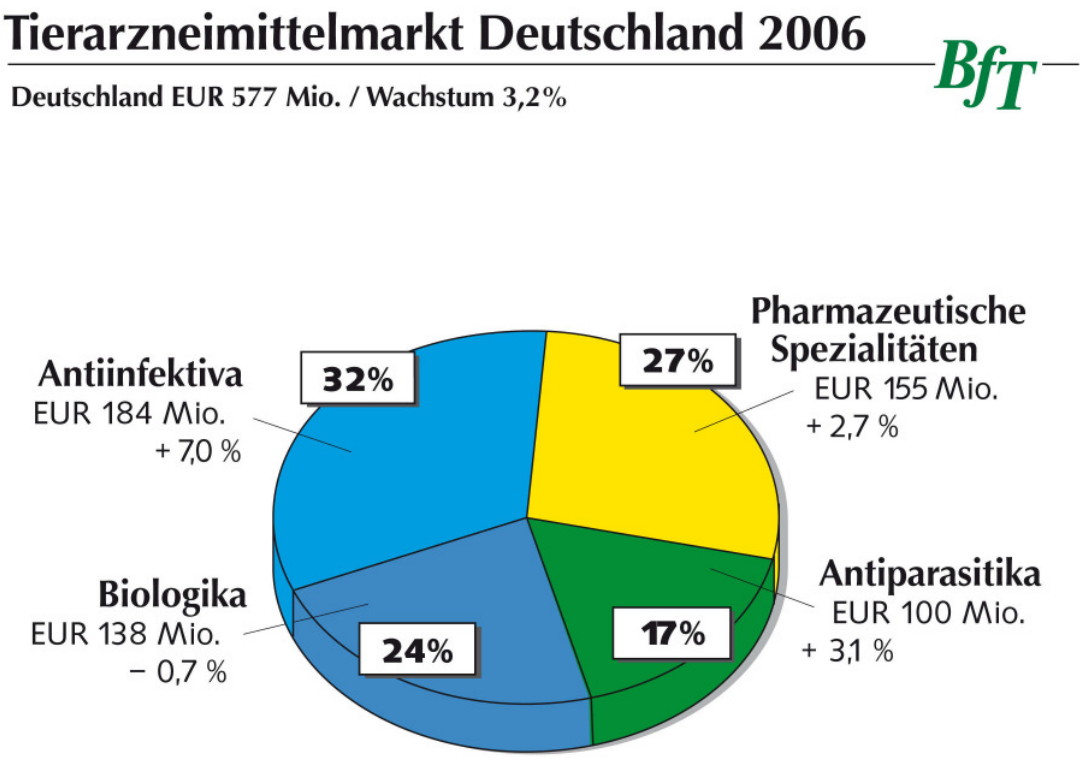
3.1.1.1. Nature of chemical compound

VMPs intended for supporting deficiency conditions in animals and containing electrolytes, vitamins, peptides and proteins, which are natural substances and anyway abundantly present in the environment, will not need to be extensively assessed.

3.1.1.2. Target Species

All VMPs to be used merely in companion animals (horses excluded) will not have to proceed to a PEC calculation. Concluding from sales volumes in Germany (Figure 4) which reveal equal values regarding small companion animals and food producing species, about half of the VMPs currently on the market are excluded from a detailed Phase I assessment. However, in the specific case of ectoparasiticides used in dogs, risk mitigation measures must be included in the SPC, otherwise additional assessment is required (5).

Figure 4: Sales volumes VMPs in Germany 2006



In case of Advocate, a spot-on solution for dogs suffering from, or at risk of mixed parasitic infection, the applicant obviously provided data on possible environmental contamination within the application dossier (29). Contamination of the aquatic environment was found to be likely and PECs of 4 µg/l imidacloprid and 1 µg/l moxidectin were estimated. The applicant further presented aquatic toxicity data and

determined PNEC data, which resulted in case of moxidectin only in an acceptable RQ, when treated animals are prevented from swimming for four days. The following wording was included into the SPC: “Dogs should not be allowed to swim in surface waters for 4 days after treatment”.

VMPs intended for use in horses will not be excluded naturally from a PEC calculation as horses are considered as a food producing species. This should also apply for VMPs merely intended for use in horses that have been excluded from human consumption, as this intention does not impact the environmental risk.

3.1.1.3. Pharmaceutical class

A comprehensive group of VMPs is exempted from further Phase I assessment by there pharmaceutical class. EMEA guidances (5) includes all anaesthetics and sedatives, injectable corticosteroids, injectable NSAIDs, hormones (except for zootechnical use), injectable antibiotics (except those likely to be used for treatment of animal groups like VMPs used in pigs and VMPs used to treat respiratory infections in cattle or foot rot in sheep).

3.1.2. VMPs for which a PEC calculation is mandatory

The current guidances basically require PEC calculation for those VMPs that are likely to be used at great amounts and in a great number of animals. In fact, those VMPs that can be expected to entry the environment at high concentrations. Consequently this includes all VMPs used for routine (group) medication or intended for use in common (endemic) conditions in intensive livestock farming, unless they have been exempted before. They all have in common to be a therapeutic against some kind of infectious disease, which by its nature is likely to affect a large fraction of a herd.

Although not exhaustive EMEA guidance (5) comprises the following to be mandatory:

- All products for poultry and for fish as they are commonly kept in groups and in general treatment will be a mass drugging.
- All anthelmintics, all coccidiostatics and ectoparasiticides (in all food producing

species) as these VMPs are used in endemic conditions and treatment is only reasonable when all susceptible individuals are included.

- All teat dips and sprays as wherever they are used they will be applied to each individual of the herd.
- All intramammary preparations as using a VMP during the drying off period is a standard treatment and mastitis during lactation is found to be a major problem in most dairy herds.
- All products for treatment of diarrhoe in calves, lambs and pigs, as diarrhoe is a severe condition and almost endemic in young animals especially when kept intensively.
- Antibiotics given as feed or water medication, as this is by its nature a treatment for large groups of animals.
- Injectable antibiotics for the treatment of respiratory infections in cattle or foot rot in sheep and moreover for all treatments in pigs. Again almost endemic situations in cattle and sheep are affected and moreover infectious diseases in pigs.

3.2. PEC calculation

Results of PEC calculation will identify those VMPs for which a phase II assessment will be mandatory. Standard values for body weight, turn over rate and treated fraction of the herd have to be utilised unless the applicant brings evidence that some other values are more appropriate for the VMP under investigation.

Naturally doses regime has a major effect on the predicted amount which is assumed to entry environment. Table 4 gives an overview on maximum doses (mg/kg) of the active per treatment (daily dose x days of treatment x bodyweight), which would not result in a PEC_{soil} above 100 µg/kg.

Values differ not only between target species but also between age groups within a species. In general doses per treatment will be considerably lower in those age groups where a high turnover rate is assumed. This becomes obvious when investigating

VMPs to be used in pigs. In weaners the PEC_{soil} is already reached at doses exceeding 12 mg/kg per treatment while sows may be treated with 48 mg/kg per treatment. The same applies for chicken, as the maximum dose per treatment in broiler is much lower than in laying hen. In cattle, where no differences in turn over rate are assumed, this effect does not exist.

Results in Table 4 refer to treatment of varying fractions of the herd considering the therapeutic class of the VMP. Lowest possible values for doses/treatment apply for parasiticide, oral antibiotics and poultry treatments as 100 % of the herd are assumed to be treated. The values increase when the VMP is only assumed to be applied to 50 %, 30 % or 25 % of the herd.

As values expressed in Table 4 are maximum dose per treatment, number of daily doses (duration of treatment) has a major impact on the maximum daily dose which would result in a PEC_{soil} lower than 100 µg/kg. In general parasiticides are given only once. Thus parasiticides given at doses below those in the table will not move into a Phase II assessment. On the other hand antibiotical treatment will in most cases continue for at least 3 to 7 days. Consequently maximum daily dose will be considerably lower than values presented in Table 4.

Table 4: Maximum dose of active component per treatment to not exceed PEC_{soil} = 100 µg/kg (in mg/kg/treatment)

	Parasiticide, oral antibiotics, all poultry treatments (100 % treated)	Injectable antibiotics in pig or for respiratory infections in cattle (50 % treated)	Products for treatment of diarrhoe in calves, lambs and pigs (30 % treated)	Intramammary preparations (25 % treated)
Calf	18	35	58	
Dairy Cow	31	62		125
Cattle (0-1 year)	20	40		
Cattle (>2 years)	17	34		
Weaner pig (to 25 kg)	12	23	38	
Fattening Pig (25-125 kg)	17	34	57	
Sow (with litter)	48	96	159	
Broiler	11			
Laying hen	97			
Replacement layer	51			
Broiler breeder	179			
Turkey	23			
Duck	16			
Horse	19			

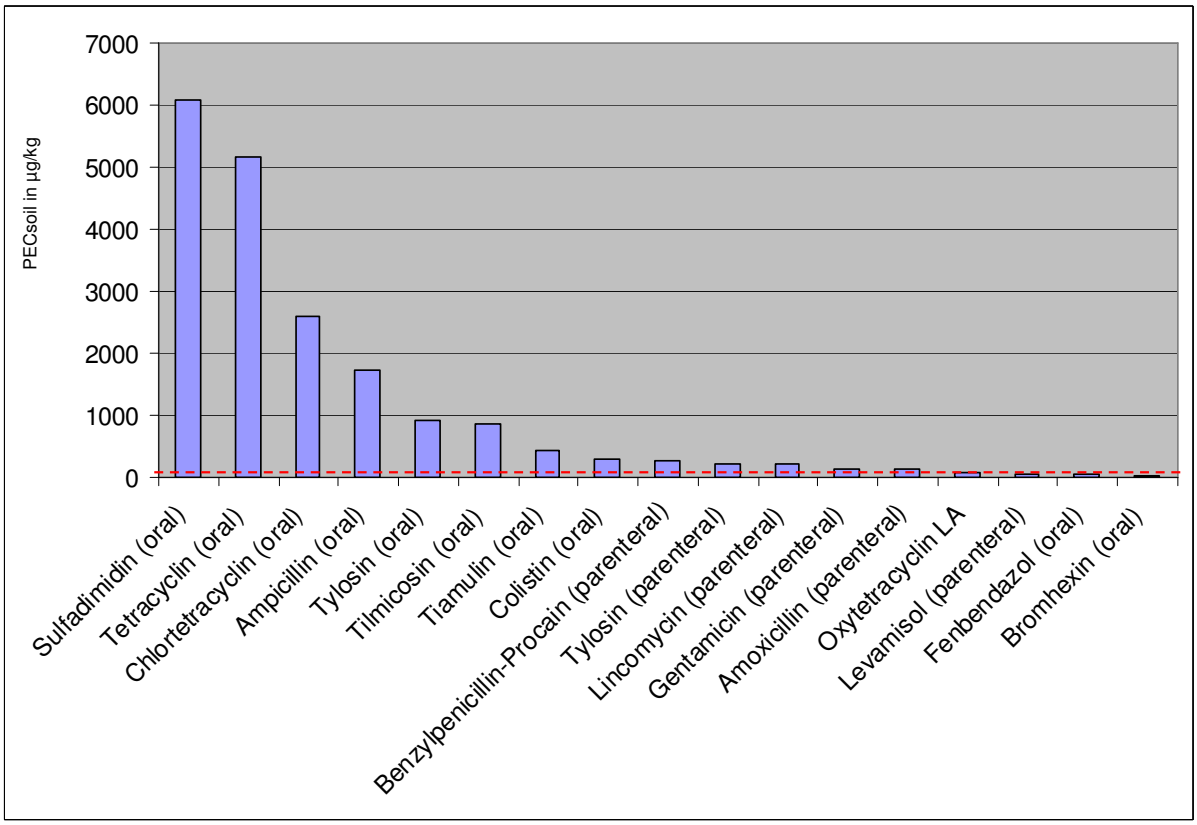
3.2.1. Pigs

The use of a VMP in weaner pigs has been identified to cause the highest predicted entry into the environment and thus being most likely to result in a PEC_{soil} beyond 100 µg/kg and stipulating a Phase II assessment (see Table 4). Therefore standard values referring to the use in weaners have been considered for exemplary PEC_{soil} calculation.

Figure 5 illustrates PEC_{soil} of a number of active substances that are used in veterinarian practice on a routine basis. Among the presented examples only VMPs

were considered that are very likely for PEC calculation (3.1.2). Values for doses and duration of treatment for weaners have been taken form product literature of VMPs authorised in Germany. The considered dose refers in each case to the salt of the active substance as it is used in the VMP unless the free molecule is used.

Figure 5: PEC_{soil} (µg/kg) of VMPs authorised for use in pigs, considering doses and treatment duration recommended for weaners of 12,5 kg body weight. PEC trigger value of 100 µg/kg is illustrated by dashed line.



The diagram illustrates that all of routinely applied oral antibiotics will exceed the PE_{soil} limit of 100 µg/kg. Parallel intake of feed is known to significantly lower bioavailability of the active substance (30, 31). However, oral medication of animals is commonly given with feed. In consequence doses of most oral VMP will be comparatively high in order to obtain therapeutic levels. This naturally results in a higher (predicted) environmental entry.

Sulfadimidin is authorised at a dose of 100 mg/kg over a period of 7 days, which results in an extreme high PEC_{soil} of more than 6000 µg/kg. Similar values are predicted for Tetracyclinehydrochlorids that are known to be absorbed only moderately (32). Recommended 85 mg/kg over 7 days (PEC_{soil} = 5170 µg/kg) make assessment of its ecotoxicity inevitable.

PEC_{soil} on the other hand will significantly decrease when lower doses are examined. Tilmicosinphosphat in oral preparations is given at 20 mg/kg for 5 days resulting in a PEC_{soil} of 870 µg/kg; while Colistinsulfat (5 mg/kg, 7 days) has a PEC_{soil} of 304 µg/kg. Moreover Bromhexinhydrochlorid is given at 0,5 mg/kg over 5 days equal to a PEC_{soil} of 22 µg/kg.

Nevertheless, parenteral preparations may also be given at amounts that result in a PEC_{soil} exceeding the limit. VMPs containing Benzylpenicillin-Procain given at a dose of 20 mg/kg to weaners over a period of 3 days will result in a PEC_{soil} 261 µg/kg. Similar values result from PEC_{soil} calculation for Lincomycinhydrochlorid (217 µg/kg) and Gentamicinsulfat (148 µg/kg). Degradation studies or further assessment in Phase II for these VMPs is therefore inevitable.

In veterinary medicine there is a tendency towards development of innovative, highly potential VMPs that are only given as a single injection. Tulathromycin (not shown in the diagram), an antibiotical compound, is given at 2,5 mg/kg once resulting in a PEC clearly below the trigger value (33). Furthermore even long known so called “long action” formulations as Oxtetracyclin LA, with a single application per average treatment (20 mg/kg) will not exceed the PEC limit (see Figure 5).

Parasiticides are usually given once. Neither of the examined preparation in pigs (Fenbendazol, Levamisolhydrochlorid see Figure 5) nor in cattle (Ivermectin, Levamisolhydrochlorid, Fenbendazol, Albendazol see Figure 6) exceeds the trigger value. Still, as at least in cattle the use of the latter on pasture is compulsive a Phase II assessment is mandatory in any case.

3.2.2. Cattle

To examine the situation in cattle exemplary PEC_{soil} calculation have been performed on the basis of standard values connected to the use of a VMP in calves. As outlined during discussion of Table 4 and different to the situation in pigs, no specific age group was identified to be the most critical in terms of potential environmental entry. However for exemplary calculation calves have been chosen, since oral medication of ruminating cattle is limited to very specific cases. Again variable values have been taken form product literature of VMPs authorised in Germany. Results are illustrated in Figure 6.

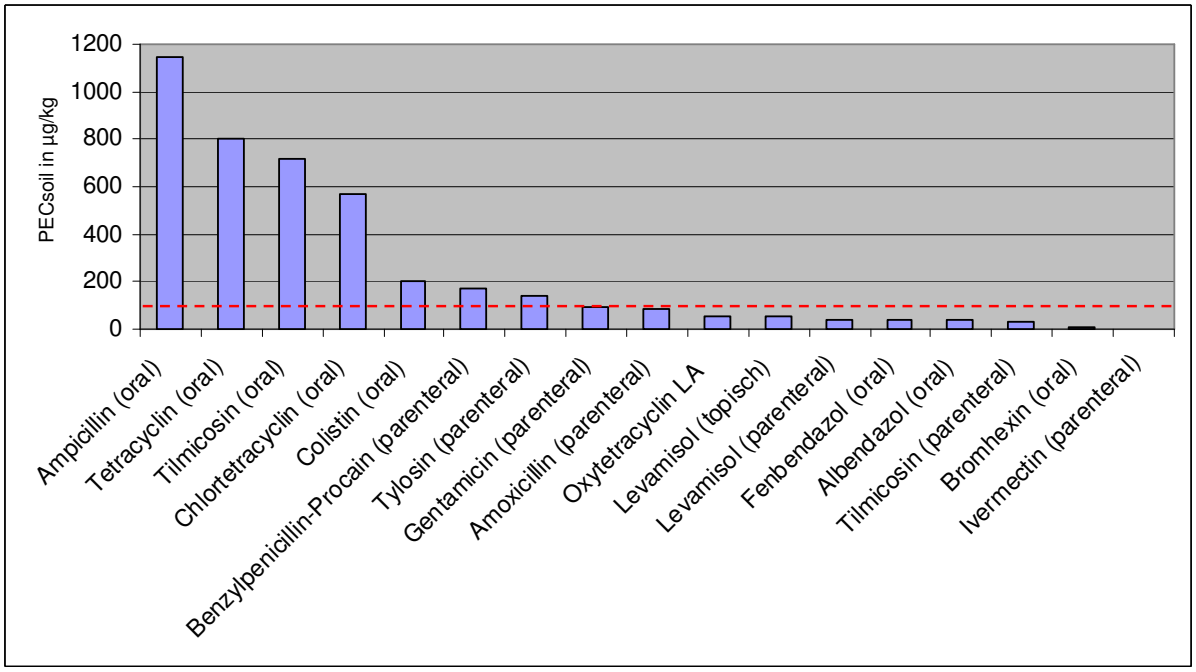
Similar to the situation in pigs the use of all common oral antibiotical treatment will result in very high PEC_{soil}. Treatment with oral antibiotics requires fairly high dosing over 3 to 7 days. The comparably high amounts of drugs will cause a high predicted entry into the environment which in all of the presented examples results in exceeding the PEC trigger value.

Compared to values estimated for weaners maximum PEC_{soil} resulting from the treatment of calves will be significantly lower. The considered SPC of Ampicillintrihydrate recommends a dosage of 40 mg/kg per os over a period of 5 days. The corresponding PEC_{soil} value is 1142 µg/kg which makes either a degradation study or even a Phase II assessment necessary. Chlortetracylinhydrochlorid and Tetracyclinhydrochlorid (20 mg/kg) are used at lower doses in calves as in pigs (60 – 80 mg/kg) and thus resulting in lower PEC_{soil}. However, predicted concentrations still exceed the trigger value by far.

In regards to parenteral antibiotics PECs of Gentamicinsulfat and Amoxicillintrihydrat will be just below the 100 µg/kg trigger value, while they exceed the latter in weaners. Thus a further assessment for indications in calves would not be necessary.

As already illustrated for pigs parasiticides commonly used in calves do not exceed the PEC limit. However, as application of ecto- or endoparasiticides to cattle reared on pasture is very common a Phase II assessment has to be considered as mandatory. In cases where the SPC clearly states that usage of the VMP is merely authorised for cattle that is kept in house (intensive rearing of beef calves) a further Phase II assessment might be avoidable.

Figure 6: **PEC_{soil} (µg/kg) of VMPs authorised for use in cattle, considering dosis and treatment duration recommended for calves of 140 kg body weight. PEC trigger value of 100 µg/kg is illustrated by dashed line.**



3.3. Degradation studies

Some VMPs that have been shown to exceed the PEC_{soil} trigger value for one or more target species or indication might be susceptible to degradation in manure. According to the guidance (5) no further Phase II assessment is mandatory if it could be proofed that the active residue is rapidly and completely degraded.

For innovative substances the concerned applicant will have to set up a suitable study design by himself, since no standard study protocol is available at present. In most cases use of a radiolabelled active will be the most advisable approach. However, comprehensive degradation studies, analysing the actives stability in each target species manure separately, will be quite cost intense. Thus the applicant might be advised to seek regulatory guidance in advance.

For existing drug substances there might be sufficient data in the open scientific literature, which could proof a rapid and complete degradation. The Danish Environmental Protection Agency has published a tabulated literature review on the issue, presenting some 20 publications on the fate of medicinal compounds in the environment (34). Presented biodegradation data showed that half-lives varies from a few days to years depending on characteristics of the active, the matrix (e. g. sol, water or manure) and on environmental conditions such as temperature, humidity and pH. However, any bibliographic evidence would need to present not only study results but sufficient details on the testing methods additionally. It might be presumed that substantial data will not be available for most of the concerned active substances.

3.4. Phase II

In Phase II data on the active's ecotoxicity to different environmental compartments are generated. VMPs acting as ecto- or endoparasiticides are most likely to undergo such a procedure since they are commonly given to pasture animals. By their nature parasiticides have a potential to harm non-target species like helminths or insects. Numerous species of the environmental fauna belong to the same zoological class. Negative effects of parasiticides on these species might be assumed. In those cases

the applicant should proof the opposite or investigate on measures that would result in minimising the risk.

All parasiticides that are used in pasture animals are mandatory for a Phase II assessment, due to the direct entry into the different ecological compartments. Individuals of most food producing species are reared outdoor at some point or in some cultural context. Industry therefore should be aware that presumably all parasiticides intended for use in food producing species need to undergo a Phase II assessment.

Regarding VMPs belonging to other pharmaceutical classes the applicant may bring evidence that the active is fully and rapidly degradated in the manure. If this is not the case or no studies on this question have been performed a Phase II assessment will be necessary.

Again there might be some data available in open literature (34). Whether this information will be sufficient has to be explored on the specific case.

4. Discussion

In Dir. 2004/28/EC introduction section it is stated that „The environmental impact (of VMPs) should be studied and consideration should be given on a case-by-case basis to specific provisions seeking to limit it" (6). Indeed current legislative assures that environmental impact of any VMP has been addressed by the applicant and assessed by the competent authorities before any marketing authorisation is granted. A systematic environmental assessment according to the regulatory guidances (5, 10) has to be element of any dossier submitted. In fact, in some cases applications have not been considered valid as long as a sufficient ERA had not been included in the dossier (personal communication).

Current regulatory guidances have established a system, which excludes a high percentage of VMPs from cost intense studies. However, it also determines numerous VMPs that have to undergo a study battery. Main criteria for selection are the absolute amounts of the active substance that are estimated to entry the environment in total. The group of critical VMPs comprehends most drugs that are used as routine medication against some infectious disease in livestock. Undoubtedly anti-infectives authorised for use against common and almost endemic diseases in today's intensive livestock rearing are sold in considerably high amounts. Relating to data from the Danish Environmental Protection Agency 48,5 tons of therapeutically used antibiotics have been sold in Denmark during 1997.

However, an approach where merely the absolute tonnages are taken into account the toxic potential of the actives is left unconsidered. Pharmaceuticals used in small doses have obviously proofed to have a great pharmacological activity in the target species. This might implicate a similar high pharmacological potency in non target species in some environmental compartment. To not consider the toxicological potential of the actives possibly leads to a situation, where VMPs with a potential of environmental harm are excluded form further investigation at very early stage. Therefore the established system seems to be susceptible to result in wrong negative assessment,

where environmental risks are not identified and no risk mitigation measures are applied.

This issue is currently discussed on the example of Ivermectin (35). Ivermectin has found to be harmful to species of the dung fauna at comparatively low concentrations. Yet, due to the small amount of active per treatment any PEC will be far below the trigger value. Concluding from the Phase I decision tree any Ivermectin containing VMP intended for in-house livestock would no be obliged to undergo a Phase II assessment nor would risk mitigation measures be established.

In fact, this does not apply for parasiticides intended for the use on pasture. They are controlled very strictly by the current legislative and are very likely to be assessed intensively.

Yet, none VMP used in small animals will be mandatory for a detailed Phase II assessment. The reasons for not applying similar criteria to these VMPs have not been communicated comprehensively. There are VMPs, e. g. parasiticides for dogs and cats, used on a routine basis and all over the country. Considerable amounts of the actives might entry the environment, while there are no scientific data are available on the possible environmental effects.

On the other hand Phase I decision might identify VMPs to be mandatory for degradation studies or Phase II assessment, which in fact are harmless to the environment. The need for cost intense studies is very likely to result in a situation where an application for marketing authorisation would be economically unattractive.

Therefore the current system might be at a risk, that filter system of Phase I fails to identify those VMPs which are in fact a harm to the environment. It appeals that selection criteria that consider the toxic potency of the active should be incorporated in the decision tree.

Although consequences of the EMEA guideline (5) might be profoundly to some marketing application some details seem not be appropriately justified. Equation for PEC estimation considers a depth of penetration of 5 cm. There is no justification for the value within the guidances. In practice volume of soil the VMP will distribute in is much higher in cases where the manure is spread on arable land, as common ploughing depth is at least 20 cm. Naturally this is different and probably less on pasture. However, since the value of 5 cm is not justified it occurs to be somewhat arbitrary.

Furthermore standard values referring to the percentage of herd that is treated have obviously been established based on discussion with veterinary surgeons in a number of Member States. As these values are essential for PEC calculation a more scientific justification should be expected.

From an industry perspective the proof of complete and rapid degradation in manure is not addressed satisfactorily. Current sight of some competent authorities demands degradation studies not only for each target species but also for each age group. Referring to a VMP intended for cattle, pigs, chicken and turkeys this would easily result in up to ten degradation studies, even if instability in an aquatic environment was already proofed in the first study. There is a need of an accepted approach permitting conclusion of one type of manure to another by introducing safety factors. Otherwise an applicant could (and in fact has) easily spend 100.000 € merely to proof that the VMP could stay in Phase I (personal communication).

Moreover results of a degradation study can not be used to alter the PEC in Phase I. This seems not in line with establishing a PEC limit. If the trigger value of 100 µg/kg is sensible to have, it should be possible to use degradation data to proof that instability of the active in manure could decrease the PEC to a value below the trigger of concern.

Introduction of inevitability of an ERA for all marketing application by Dir. 2004/28/EC (6) does result in the need of assessment of numerous VMPs. The provisions of an ERA do not merely apply to innovative VMPs anymore. Any application even for active compounds that have been used for decades has to assess the environmental risk according to the guidelines. According to Article 13 of Dir. 2001/82/EC as amended (11) an applicant can not refer to the data on environmental fate and effects of the reference dossier, but has to bring sufficient data independently. This seems to be contrary to the generic idea and might lead to parallel conduction of similar studies on ecotoxicity by different applicants. This is not very economic and is at risk that the different studies would suggest different conclusions. Therefore it would be sensible for industry to form alliances similar to establishment of the maximum residues in 1990s. Different to this project a system must be found, where the data are not made available to public, but only to those applicants that have or are willing to financially contribute to the studies. This kind of monograph system has to be set up by industry as the regulatory bodies seem not willing to offer the coordination of the latter. In any case there must be a system of data protection for the ERA data, to ensure that applicants have a change of reimbursement of their costs.

5. Summary

The use of VMP is likely to result in an exposure of the environment to pharmacological active substances, as not all active ingredients will be completely metabolised in the treated animal. Pharmacological potential of some active substance might be harmful to one or more non-target species, might it be microbes, plants or animals, and thus result in negative effect on the environment. This ecotoxical potential of a VMP has to be assessed by the applicant and the results presented in the marketing application dossier. In order to characterise the effect on the environment and to identify possible risk mitigation measures the assessment has to follow a common standardized approached, which has been published in EMEA guidances. The guidelines establish a system, which excludes a high percentage of VMPs from cost intense ecotoxical studies. For these VMPs the applicant merely has to bring evidence, that the active is a natural substance or is not expected to enter the environment at great amounts. VMPs that are likely to be used in a high number of animals and at high doses are expected to entry the environment at great amounts and thus investigation on their ecotoxical potential has to be performed by means of a study battery. Basically this group of critical products is formed by VMPs that are indicated for the use in almost endemic infectious diseases in intensively reared animals or used as parasiticides in pasture animals. Until now neither the pharmacological nor the toxicological potential of the active are considered, which results in a risk of not identifying highly ecotoxical substances.

The environmental risk assessment itself is based on a risk quotient approach, where the risk quotient is determined by the ratio of the predicted environmental concentration and the predicted no effect concentration. Only a risk quotient exceeding the value of one will lead to acceptance of the VMP, in other cases suitable risk mitigation measures have to be introduced by the applicant or in a worst case the application will be refused.

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Hiermit erkläre ich an Eides Statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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