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Guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38

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[1] Page 29: Equation 13 has been added showing how $PECsoil_{single\ event}$ is calculated.
Page 43: Equations 33, 34 and 35 are added.
Page 54: Stream flow value removed from Table, as it is not considered necessary for the calculation
Page 58: The number of sheep to be considered for Equation 53 has been added.

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EXECUTIVE SUMMARY

This supporting guideline should be read and used in conjunction with VICH GL 6 (Phase I) and VICH GL 38 (Phase II). The purpose of this guideline is to provide additional, more specific technical guidance on environmental impact assessment in areas, where the VICH guidelines are more general or refer to further regional guidance, but not adding new requirements or deviating from the VICH guidelines. In the supporting guideline algorithms, models and default values are presented for the determination of the concentration of a veterinary medicine in the environment. The guideline is intended to facilitate the preparation of the environmental risk assessment part of marketing authorisation dossiers and to harmonise the interpretation of the VICH guidelines by Member States, thus strengthening predictability and transparency of the outcome of an environmental impact assessment.

For reasons of accessibility, the questions structure of Chapter 5 (Phase 1) and the numbering of the paragraphs in Chapter 6 (Phase II) has been aligned with the structure used in the VICH guidelines.

Experience of the environmental risk assessment process will obviously come from evaluation of assessments. Comments from users of the VICH guidelines and/or this guideline are welcomed. Such comments may be addressed to the European Medicines Agency (EMA).

1. INTRODUCTION

The requirement for assessment of environmental safety for Veterinary Medicinal Products (VMPs) was introduced into the legislation by Directive 92/18/EC [1]. Since that time data on ecotoxicity have been required as part of the safety submission for a Marketing Authorisation (MA).

The Directive stated that the environmental assessment should be carried out in two phases. In the first phase the extent of environmental exposure should be estimated while in the second phase the fate and effects of the active residue should be assessed. The basic framework provided by the Directive was elaborated by guidelines published by CVMP in 1997, providing guidance to both applicants and to the regulators on how the assessment of environmental safety should be carried out.

The CVMP guidelines have in the meantime been replaced with VICH guidelines: Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products - Phase I [2] published in 2000; CVMP Guideline on Environmental Impact Assessment for Veterinary Medicinal Products - Phase II [3], published in 2004.

2. SCOPE

In addition to the VICH guidelines this supporting guideline has been prepared to:

1. Provide guidance for those points where VICH guidelines recommend asking for (regional) regulatory guidance.
2. Provide for a harmonised approach for the assessment of environmental safety, independent of the application procedure (centralised, decentralised, mutual recognition or national marketing authorisation application).

This guideline covers areas of expertise which are still evolving. Therefore, it is envisaged that there will be a need for updates of the guideline and flexibility of approach.

3. LEGAL BASIS

This guidance document is only applicable for the assessment of pharmaceuticals.

Directive 2001/82/EC, as amended by Directive 2004/28/EC [4] as well as Regulation (EC) 726/2004 [5], include new provisions regarding the consideration of effects on the environment in the benefit/risk assessment of veterinary medicinal products and on the data requirements regarding such effects. An environmental risk assessment is therefore mandatory for all new applications, independent of the application procedure (central or national marketing authorisation) and type ("full", "generic" etc.) and is therefore required for all marketing authorisations submitted in the EU irrespective of the underlying legal basis.

In respect to renewals the legal provisions under Article 28(2) of Directive 2001/82/EC and Article 39(2) of Regulation (EC) No 726/2004 require "a re-evaluation of the risk-benefit balance". The risk-benefit balance as defined in Article 1(20) of Directive 2001/82/EC includes an evaluation of the risks referred to in Article 1(19), which in turn includes "any risk of undesirable effects on the environment".

Further guidance on the interpretation of the data requirements under Article 12(3)(j) in particular in respect to marketing authorisation applications for generics, extensions and variations, as well as for renewals is being developed.

3.1 RISK MITIGATION MEASURES

Risk mitigation is an essential part of the evaluation of products; risk mitigation can be used to restrict the risk associated with a product to an acceptable level, or even to completely remove such a risk. In principle, the applicant should propose risk mitigation measures and, if appropriate, the efficacy of such measures should be substantiated by data in the dossier. Sometimes (e.g. in case of removing an indication or even target animal from the label) such a proposal may remove the need for further testing.

If the use of a product results in an unacceptable risk for the environment, then mitigation measures should be proposed by the applicant in order to reduce the risk to an acceptable level: Article 12 (3)(j) of Directive 2001/82/EC as amended requires "the results of tests assessing the potential risks posed by the medicinal product for the environment. This impact shall be studied and consideration shall be given on a case-by-case basis to specific provisions seeking to limit it."

To be effective such a risk mitigation measure should meet the following criteria: It should

- Mitigate exposure of the VMP to the environment
- Be in line with agricultural practice
- Be in agreement with the legislation of the EU and its Member States
- Be possible to demonstrate the effect of the proposed risk mitigation measure by re-evaluating the exposure assessment with the proposed risk mitigation measure included

If a risk mitigation measure does not fulfil the criteria mentioned above then the outcome of the risk assessment is that a serious risk for the environment exists. In accordance with Directive 2001/82/EC (as amended) this risk has to be weighed against the favourable aspects of a marketing authorisation.

The Guideline on the Summary of Product Characteristics (SPC) for Pharmaceutical Veterinary Medicinal Products, NTA, Volume 6C gives a number of examples of possible risk mitigation measures:

"The product should not be allowed to enter surface waters as it has harmful effects on aquatic organisms."

"Do not allow treated animals to swim in watercourses until at least x hours/days after administration."

"*XX should not come into water courses as this may be dangerous for fish and other aquatic organisms."*

"*The long-term effects of* YY *on the population dynamics of dung beetles have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season.*"

4. Structure of the environmental risk assessment of veterinary medicinal products

Risk assessment is an evaluation of the possible fate, exposure and effects of the product. As a whole, the risk assessment is structured around the risk quotient approach as described in VICH guidelines GL6 (Phase I) [2] and GL38 (Phase II) [3]. The risk quotient (RQ) is defined as the ratio between the predicted environmental concentration (PEC) and the predicted no-effect concentration (PNEC). If reliable monitoring data are available, these may replace the predicted values. The risk quotients indicate the likelihood of adverse effects occurring.

In Phase I, the investigator shall assess the potential extent of exposure of the environment to the product, its active substances and other ingredients, taking into account:

- The target species, and the proposed pattern of use
- Characteristics of the constituents of the VMP
- The method of administration

In Phase I several exemptions from further testing are incorporated. When these exemptions do not apply, and trigger values are exceeded, one enters Phase II. Furthermore, if adverse environmental effects are anticipated from the use of products, further assessment of possible exposure of the environment can be performed, even if straightforward application of the Phase I guidance would indicate exemption from further testing. The Introductory section of VICH GL6 clearly states "Some VMPs that might otherwise stop in Phase I may require additional environmental information to address particular concerns associated with their activity and use. These situations are expected to be the exception rather than the rule and some evidence in support of the concern should be available".

According to Directive 2001/82/EC [4],

> *"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".

As appropriate, further investigation may be required of:

- Fate and behaviour in soil, water and dung
- Effects on aquatic organisms
- Effects on other non-target organisms

The Phase II assessment starts at Tier A with a base data set on fate and effects that allows for risk characterisation. If a risk cannot be excluded the assessment proceeds to Tier B. The VICH documents present a set of Phase II Tier B fate and effects studies. This guidance document provides suggested studies, where none are given in the VICH document. In addition some alternative studies to those presented in VICH are also listed.

4.1. Data requirements

To assist the environmental impact assessment all information relevant to the evaluation of the medicinal product shall be included in the application, whether favourable or unfavourable to the product (see Annex I of Directive 2001/82/EC, as amended). That includes also any incomplete or abandoned test or trial relating to the veterinary medicinal product. Moreover, after marketing authorization, information not in the original application, pertinent to the benefit/risk assessment, shall be submitted forthwith to the competent authority.

Published data provided should follow the guidance on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products[2]. Copies of published data should be appended to the proprietary data and all proprietary data should be discussed in conjunction with the data from the open literature.

The information needed for the Phase I and Phase II assessments is discussed in the Evaluation Chapters. All information is evaluated and summarised so as to determine its reliability and usefulness.

4.2. Release estimation

Directive 2001/82/EC as amended [4] requires an environmental risk assessment for the use of a veterinary medicinal product, but not for the production and the waste. The environmental risk assessment of immunologicals and GMO-containing veterinary medicines is not covered by the VICH guidelines. The possible development of resistance of natural populations of micro-organisms is also not part of this guideline.

The route and quantity by which a VMP enters the environment determines the type of assessment (Phase I or Phase II) and the scenarios to be used. Dosage, route of application, type of target animals, excretion, route of entry into the environment and agricultural practice all influence the point at which environmental exposure occurs. The main scenarios are:

- Removal of material containing the product (manure, dirty water, fish farm effluent)

[2] Guidance included in the Draft CVMP Reflection paper on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products (EMEA/CVMP/182112/2006) is intended to be published in the Notice to Applicants, Volume 6, once finalised.

- Excretion via faeces and urine (grazing animals)
- Spillage at external application and/or direct exposure outdoors

In Phase I a 100% release to the environment will normally be assumed (total residue approach). The total residue approach does also apply to externally applied products irrespective of the behaviour of the molecule following administration. External application is indicated for pour-ons, sheep dips, fumigation, udder disinfectants, etc. Use of products by external application may result in the product being found in manure and/or in washings from dairy parlours and pig and poultry stables due to cleaning of the pens[3]. If there is no direct route to the manure (spilling, shedding from skin), there may be adsorption through the skin and subsequent excretion. In that case the pathways for internal administration should be considered. The fractions of externally applied products, which enter the environment via different routes should sum to 100% to provide a total residue approach. Functions and uses not considered here are dealt with on a case-by-case basis.

Based on the husbandry conditions described in Chapter 5, the following possible exposure routes are identified (Table 1).

Table 1. Predominant exposure routes of veterinary medicines in key livestock species.

Livestock category	Slurry application	Grazing animals	Loss at application/ exposure outdoors	Direct entry into water*
cattle	X	X	X	X
pigs	X			
horses and ponies	X	X		
sheep/goats		X	X	X
poultry	X			
fish farms	X			X

* this can mean direct excretion, loss from the fleece/hide or direct entry of the veterinary medicine

4.3. Environmental distribution

The route of distribution and the fate in the environment are important for the final exposure concentration. For veterinary medicinal products, the predominant routes of exposure for the terrestrial and aquatic environment are through the application of manure, dung and urine. Distribution of the product occurs within the directly exposed compartment(s) and between different compartments.

The terrestrial environment is exposed via:

1. Direct excretion of dung and urine;
2. Loss from animals treated topically;
3. Spreading of contaminated slurry and/or sludge.

The aquatic environment is exposed via:

1. Leaching, run-off and drainage from manured land;
2. Direct spillage and/or feed spillage;

[3] These washings, called 'dirty water' generally contain <3% dry matter, and are made up of water contaminated by manure, urine, silage run off, milk, other dairy products and cleaning materials.

3. Direct excretion into water (pasture animals);

4. Direct application in water (aquaculture);

5. Direct discharge of waste water into surface water (indoor aquaculture);

6. Release from Sewage Treatment Plants (indoor aquaculture).

During distribution the active ingredient can be incorporated into soil or sediment material as bound residues or transformed to metabolites or carbon dioxide. Mineralisation or degradation to substances that are part of biochemical pathways are considered as endpoints in biodegradation studies.

Often metabolites of organic compounds are more hydrophilic than the parent compound, as a result of which they will be more susceptible to leaching to groundwater. This effect might be overlooked in a "normal" total residue approach. Therefore, data for the metabolite(s) may be required if such a request can be justified scientifically.

Exposure of birds and mammals through application of veterinary medicinal product residues is possible. Because these non-target species are exposed to the products via their feed and water, calculations are performed to translate concentrations in compartments to concentrations in the feed.

5. Phase I guidance (VICH GL 6)

EXPLANATORY NOTE on Phase I Guidance

This guidance is provided in addition to guidance provided in the CVMP/VICH Topic GL6: Environmental impact assessment (EIAS) for veterinary medicinal products - Phase I (CVMP/VICH/592/98-FINAL). Therefore, this chapter should be read in conjunction with the mentioned guideline. For legibility and easy navigation this section has the same structure as found in the CVMP/VICH guideline (i.e. *Question 1*. refers to VICH GL 6 *Question 1.*).

Question 1. - *Is the VMP exempt from the need for an EIA by legislation and/or regulation?*

In accordance with the legislation an assessment of environmental safety is required for all applications for a Marketing Authorisation.

It should be noted that there are categories of products, which are considered to be VMPs in some MS but not in others. For example teat dips in some MS are not considered to be VMPs, but in others they are classed as VMPs.

Question 2. - *Is the VMP a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment?*

No additional guidance on top of that provided in the VICH Phase I guidance document is necessary.

Question 3. - *Will the VMP be used only in non-food animals?*

In a decision tree the questions are dealt with in a specific logical order. This means that because of the exclusion of non-food animals in Question 3 no further assessment will be required, in principle, for

these species. In the specific case of ectoparasiticides applied topically to dogs, the risk mitigation measure given in the SPC guideline (Guideline on the Summary of Product Characteristics Pharmaceutical Veterinary Medicinal Products, NTA, Volume 6C, section 4.5.iii) should be used, otherwise additional assessment is required.

Question 4. - *Is the VMP intended for use in a minor species that is reared and treated similarly to a major species for which an EIA already exists?*

In the context of this question the major species are considered to be the major food species: cattle, pigs, chickens, sheep (meat), Atlantic Salmon. All other food species are considered "minor".

Question 5. - *Will the VMP be used to treat a small number of animals in a flock or herd?*

Depending on the product and the indications for use, treatment of food animals may involve administration of the VMP to a few individual animals in a flock or herd, administration to 100% of the animals and all values in between. In the absence of published or field trial data the following product types can be considered as being used for treatment of "a small number of animals" and the Phase I assessment can end at this question:

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

It should be remembered that justification that the product is used in a way which satisfies one of the above criteria should be provided in the Phase I assessment report. It follows that for all other product types this question is not a reason to end the assessment at Phase I.

Question 6. - *Is the VMP extensively metabolised in the treated animal?*

No additional guidance on top of that provided in the Phase I guidance document is necessary. The term "a properly conducted study" refers to an absorption, distribution, metabolism, and excretion (ADME) study in the target species conducted in accordance with Volume 8 of the Rules Governing Medicinal Products in the EU.

Question 7. - *Is the VMP used to treat species reared in the aquatic or in the terrestrial environment?*

No additional guidance on top of that provided in the Phase I guidance document is necessary.

Aquatic Branch

Question 8. - *Is entry into the aquatic environment prevented by disposal of the aquatic waste matrix?*

It is considered unlikely that the answer to this question can be 'yes'. If it is considered that the assessment can stop at this question then the EIA should provide adequate justification for considering that all the waste matrix is disposed of on every occasion.

Question 9. - *Are aquatic species reared in a confined facility?*

No additional guidance on top of that provided in the Phase I guidance document is necessary.

Question 10. - *Is the VMP an ecto and/or endoparasiticide?*

No additional guidance on top of that provided in the Phase I guidance document is necessary.

Question 11. - Is *the environmental introduction concentration (EICaquatic) of the VMP released from aquaculture facilities less than 1 µg/L?*

It should be noted that the EIC should be considered as the concentration in effluent. Following the principles of the total residue approach the EIC is equal to the recommended dose, given in µg/l.

Question 12. - *Do data or mitigations exist that alter the EICaquatic?*

No additional guidance on top of that provided in the Phase I guidance document is necessary.

Question 13. - *Is the recalculated EICaquatic less than 1 µg/L?*

No additional guidance on top of that provided in the Phase I guidance document is necessary.

Terrestrial Branch

Question 14. *- Is entry to the terrestrial environment prevented through disposal of the terrestrial waste matrix?*

If it is considered that the assessment can stop at this question then the EIA should provide adequate justification for considering that the entire waste matrix is disposed of on every occasion.

Question 15. *- Are animals reared on pasture?*

The answer to this question will depend on the type of product and the indications. If the animals are on pasture during and after treatment so the active residue reaches the environment directly in excreta the answer to this question will generally be 'yes'.

Question 16. *- Is the VMP an ecto and/or endoparasiticide?*

VICH GL6 specifies that products used to treat infestations by protozoa are not captured in this question. To allow the assessment to stop at this stage, the applicant should provide a clear listing of the indications and protozoal species concerned.

Question 17. *- Is the predicted environmental concentration of the VMP in soil (PECsoil) less than 100 µg/kg?*

In Phase I the total residue approach is applied. This means that the total amount of the dose applied is excreted from the animal and data on metabolism/excretion should not be taken into account. Food producing species can be raised indoors for all or a major part of their lives or they can be kept outdoors for all or a major part of their lives. In the VICH guideline the former are considered to be intensively reared animals and the latter pasture animals. This convention has been followed in this guideline.

The calculation of the initial PEC in soil is performed when more than a "small number of animals" are treated. The proportion of animals in the herd which are treated may be available from information in the dossier such as field trial data or from the scientific literature. When such specific information is not available then the default values given in Table 2 should be used.

Table 2. Percentage herd treatment for various groups of VMPs*

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

Intensively reared animals

Intensively reared animals are those which are housed indoors throughout the production cycle so treatment with the VMP is carried out in housing and the active residue is excreted in the stable and is incorporated in the manure. This active residue reaches the environment when the manure from the stable is spread onto land.

Calculation of the $PEC_{soil\ initial}$ for intensively reared animals is dependent on the quantity of manure containing active residue, which can be spread onto land. Based on the EUROSTAT database a nitrogen load of 170 kg N /ha is on average the maximum load in most EU countries.

The $PEC_{soil\ initial}$ should be calculated using the following equation:

$$PEC_{soil\ initial} = \left(\frac{D \times Ad \times BW \times P \times 170 \times Fh}{1500 \times 10000 \times 0.05 \times Ny \times H} \right) \times 1000 \qquad \text{Equation 1}$$

where:

$PEC_{soil\ initial}$ = 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 [$place^{-1}.y^{-1}$] (see Table 3.)

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 equation the only inputs required from the user are the dose rate and the number of administrations of the veterinary medicine in a course of treatment. These parameters will be available from the product's SPC.

The number of animals raised per place per year, the bodyweight of the animal type, the nitrogen excretion values and housing factor can all be obtained from Table 3. The data in Table 3 are taken from a publication by Montforts [6] with three exceptions, the values for weaner pigs, replacement layers and broiler breeders which are from Smith and Frost [7] and Smith et al [8] and the values for rabbits are from CORPEN [44].

Table 3. Default values for use in calculating the PEC_{soil} for intensively reared animals

Animal type	Number of animals raised per place per year	Bodyweight (kg)	Nitrogen produced in 1 year per place ($kg.N.y^{-1}$)	Housing factor[1]
Calf	1.8	140	10	1
Dairy cow	1	425	60	0.5
Cattle (0-1 year)	1	200	18	0.5
Cattle (>2 years)	1	450	35	0.5
Weaner pig (to 25 kg)	6.9	12.5	2.25	1
Fattening pig (25-125 kg)	3	65	7.5	1
Sow (with litter)	1	240	26[2]	1
Broiler	9	1	0.23	1
Laying hen	1	1.6	0.35	1
Replacement layer	2.6	0.8	0.24	1
Broiler breeder	1	1.7	0.69	1
Turkey	2.7	6.5	0.9	1
Duck	7	1.6	0.41	1
Horse	1	400	35	0.5
Rabbit	8	1.4	0.352	1

[1] This term has been included in the equation to account for the fact that some animal types spend some time of the year in housing and some time on the pasture. In the PEC calculation it is assumed that the animal is treated during the period it is in housing and that the total dose is excreted in housing. The dose will then reach the environment when manure is spread

[2] This value has been corrected from the value in the paper by Montforts [6] as there was a transcription error from the original source data

Pasture animals

Pasture animals are those, which are on pasture throughout the production cycle so treatment with the veterinary medicine is carried out in the field and the residue of the veterinary medicine, is excreted directly onto the soil.

Calculation of the $PEC_{soil\ initial}$ for pasture animals is dependent on the number of animals kept on any area of land. This parameter is known as the stocking density and is expressed in animals per hectare.

The $PEC_{soil\ initial}$ should be calculated using the following equation:

$$PEC_{soil\ initial} = \left(\frac{D \times Ad \times BW \times SD \times Fh}{1500 \times 10000 \times 0.05} \right) \times 1000$$ Equation 2

where:

$PEC_{soil\ initial}$ = 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 day of treatment [d]

BW = Animal body weight [kg_{bw}.animal^{-1}] (see Table 4.)

SD = Stocking density [animal.ha^{-1}] (see Table 4.)

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]

1000 = Conversion factor [1000 µg.mg^{-1}]

Table 4. Default values for use in calculating the PEC_{soil} for pasture animals

Animal type	Stocking density (animals.ha^{-1})[1]	Bodyweight (kg_{bw})[2,3]
Dairy cow	3.5	600
Beef cattle	9.5	330
Sheep (adult ewe)	15	80
Lambs	25	36
Horse	3	600
Pony	5	250
Goat	15	60
Red Deer (stag)	15	110

[1] Data on stocking density are from RIVM reports [9] and [10] except deer and goat which are based on sheep.

[2] Data on body weight are also from [9] and [10] except for goat (British Goat Society, www.allgoats.com) and red deer (British Deer Farmers Association, www.bdfa.co.uk)

[3] These are bodyweights at turn out on pasture, so do not necessarily compare with those in Table 3.

Dairy cattle teat dips or sprays

Dairy cattle are usually treated after milking with an antiseptic teat dip. In some EU Member States these products are authorised as veterinary medicines. Teat dips are applied by dip or spray in the milking parlour and as a result a proportion of the product is lost immediately from the teats onto the parlour floor. This product will enter the dirty water[4] system of the farm and will reach the soil environment when the dirty water is spread onto land.

The $PEC_{soil\ initial}$ resulting from spreading dirty water should be calculated using the following equation:

$$PEC_{soil\ initial} = \left(\frac{V \times Md \times Dl \times C \times Fd \times 50000}{Wp \times 365 \times 1500 \times 10000 \times 0.05} \right) \times 1000$$ Equation 3

[4] Dirty water is waste, generally less than 3% dry matter, made up of water contaminated by manure, urine, silage run off, milk and other dairy products or cleaning materials.

where:

$PEC_{soil\ initial}$ = Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$]

V = Volume of dip used at each milking [$ml.cow^{-1}$]

Md = Number of milkings per day [$2\ d^{-1}$]

Dl = Number of days a dairy cow is lactating [$300\ d.y^{-1}$]

C = Concentration of active in the product [$mg.ml^{-1}$]

Fd = Fraction of dip entering dirty water [value between 0 and 1]

50,000 = Spreading rate for dirty water [$l.ha^{-1}$]

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]

Wp = Volume of water used to wash milking parlour [$18\ l.cow^{-1}.day^{-1}$]

365 = Days in one year [$d.y^{-1}$]

1000 = Conversion factor [$1000\ \mu g.mg^{-1}$]

In this equation the only inputs required from the user are the volume of dip used per cow per milking, the concentration of active in the dip and the fraction of dip entering dirty water. These values should be available in the dossier.

For this type of product only a proportion of the dose will end up in the dirty water. It is important to account for all other potential routes of exposure, i.e. in manure or directly onto the pasture when calculating the $PEC_{soil\ initial}$ for teat dips.

This equation is only for use when the product is teat dip or spray used routinely every day on lactating dairy cattle. For products administered topically to the teats which are not in this category either the equation for intensively reared animals or that for pasture animals should be used.

Fixed combination products

In the CVMP guideline on fixed combination products (EMEA/CVMP/83804/2005) [11] it states "Environmental Impact Assessment should be targeted at the effects of the combination product. If scientifically justified, data in accordance with VICH Phase I and Phase II guidelines might be provided for the individual substances only". In light of this advice should a fixed combination product reach this point in the decision tree where it is necessary to calculate a $PEC_{soil\ initial}$ value the individual $PEC_{soil\ initial}$ values for each of the active ingredients should be summed and this value should be compared to the trigger value. In situations when the summed $PEC_{soil\ initial}$ is equal to or greater than 100 µg/kg, a Phase II assessment should be conducted for all the active ingredients (see section 2.4). However, it should be noted that a Phase II assessment is not necessary if the applicant can provide a scientific justification as to why the summing of the individual $PEC_{soil\ initial}$ values is not appropriate for the particular combination under consideration. If an acceptable justification is provided no further assessment in Phase II is necessary. For example, compounds from different chemical classes which are expected to affect different taxonomic groups.

Question 18. *- Do any mitigation exists that alter the PECsoil?*

As a part of the Phase I assessment data on degradation of the active residue in manure may be submitted. If the active residue is rapidly and completely degraded in manure then the assessment may be ended at Phase I. In order to fully satisfy the requirements complete degradation, demonstrated either by total mineralisation or by the presence of degradation products all representing 5% or less of the dose, has to be achieved, to be in compliance with the definition of extensive metabolism (see question 6).

There are at present no guidelines for degradation studies in manure. If data are to be provided they should satisfy these criteria:

- The test should be carried out using radiolabelled material although unlabelled test compound may be used if justified;
- It is important when using unlabelled compound that 70-110% of the dose can be accounted for at all time points in the experiment;
- The test should be carried out in the manure of the target species;
- The relevant temperature for the test manure is 20°C for pigs, 10°C for cattle and 25°C for chickens and horses. Tests at other temperatures are accepted within a range of round 10°C, using the Arrhenius equation to recalculate the half-life. In the absence of specific information a default activation energy of 68.9 kJ mol^{-1} (and a Q_{10} of 2.8 derived from the Arrhenius equation) is recommended based on an updated opinion of EFSA for pesticides [12];
- The manure from pigs and cattle should be incubated wet/anaerobic; manure from chickens should be incubated dry/aerobic;

The degradation study should be carried out over a period of 30 days. This is a maximum value as it is considered that most manure would be stored for a certain time before spreading onto the soil. If no degradation has been recorded by the end of this time period then degradation cannot be used to mitigate the $PEC_{soil.}$

Data from metabolism and excretion studies carried out in the target species, data from soil manure mixture studies and data from bioassays are not acceptable for the refinement of the PEC_{soil} at this stage in Phase I. PEC refinement in Phase II can make use of information from these types of study.

Question 19. *- Is the recalculated PECsoil less than 100 µg/kg?*

The only possible ways for excluding a product from Phase II are given in question 6 and question 18.

6. Phase II guidance (numbering as in VICH GL 38)

EXPLANATORY NOTE on Phase II Guidance

At the beginning of Phase II 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/or risks associated with the use of the product.

At this point, it is important to make use of all available documentation relevant to the environmental risk assessment of the product. This includes physico-chemical data, relevant pharmacological-toxicological and toxicokinetic studies and information on degradability or persistence of the active ingredient[5] under relevant conditions. In respect to published data provided guidance is available)[6]. Specifically, the guidelines and test protocols issued by the European Commission [13] and OECD [14] for testing of chemicals are to be followed whenever possible. Only valid and plausible test results should be used in the environmental risk assessment and the principles of Good Laboratory Practices should apply whenever possible.

Phase II Tier A of the environmental risk assessment inevitably begins with a more detailed evaluation of exposure of the environment to the active ingredient of the VMP. The exposure of soil should consider spreading of slurry, farmyard manure and dirty water. Direct exposure of soil from animals on pasture should also be considered.[7] Exposure of the aquatic environment should consider run off and leaching of active ingredient to surface waters and groundwater as well as other routes of exposure of the aquatic environment such as cattle entering water to drink and sheep crossing water after treatment. For fish farms there will be direct exposure of the aquatic environment, but there may be exposure of the soil from spreading of sludge from holding tanks. There is a need to determine the degradation half-life of the active ingredient in the environmental compartments of interest. During this part of the evaluation, the physico-chemical properties of the active ingredient and the influence of light, pH, humidity and other factors should be taken into account. The kinetics of the elimination of the active ingredient from the environmental compartments of interest will provide valuable information about its environmental fate.

Consistency of assumptions and default values with regard to Phase I and II.

- Body weights: The body weights given for Phase I should be used in Phase II.
- Ploughing depth: In some countries manures are mainly spread on and mixed into arable land used for crop production, e.g. Belgium, Denmark, Finland, France, Germany, Italy and Spain. In other countries, e.g. Greece, Ireland and UK, it is common practice to distribute manure directly onto grassland [15]. These differences prevent a general refinement of the 5 cm mixing depth used in Phase I.
- The total residue approach which is applied in Phase I may be refined at the end of Tier A, e.g. subtracting metabolites below 10% from the total or by characterising the risk for metabolites.

The applicant should take all the above factors into account when assessing the possible accumulation and subsequent effects of the active ingredient in relevant environmental compartments. The environmental risk assessment can be concluded at Phase II Tier A if the RQ values are <1. If demonstration of an acceptable risk cannot be made in Phase II Tier A then assessment of the specific scenarios where the risk is not acceptable has to continue in Phase II Tier B. Emission into the air will be negligible for the vast majority of substances.

The following parts of this chapter should be read in conjunction with VICH Guideline 38 Environmental Impact Assessment for Veterinary Medicinal Products Phase II Guidance. For legibility and easy navigation the sections containing guidance pertaining to the different sections in the VICH guideline have the same numbering system as found in the VICH guideline (i.e. paragraph 3.3.3.1 refers to VICH

[5] It is recognised that in some cases information will be required/produced on metabolites of the active ingredient. The use of the term 'active ingredient' in the text should also be taken to imply metabolites as necessary.
[6] Guidance included in the Draft CVMP Reflection paper on the implementation of Directive 2001/82/EC, as amended, in respect to the assessment of environmental risks of veterinary medicinal products (EMEA/CVMP/182112/2006) is intended to be published in the Notice to Applicants, Volume 6, once finalised.
[7] In nearly all cases some if not all of these routes will have been considered in the Phase I assessment.

GL 38 paragraph 3.3.3.1). There are sections in the VICH guideline, which are self-explanatory, and no additional guidance is necessary. In these cases the relevant section heading has not been included in this chapter.

2.4 Risk Quotient (RQ) Approach

The VICH guideline states "The RQ (PEC/PNEC) is compared against a value of one, and a value less than one indicates that no further testing is recommended. However, in some circumstances, professional judgement is needed for a final determination."

In the context of that statement in the VICH guideline there are two particular instances where it is considered possible that an RQ of <1 may not indicate that the risk is acceptable. These situations will need to be considered on a scientific basis where professional judgement will play a key part.

The first instance is that of fixed combination products where according to the fixed combination product guideline (EMEA/CVMP/83804/2005) [11] the assessment should be targeted at the combination. A situation could arise where for a particular test species the RQ values for each of the active ingredients individually is lower than 1, but where the sum is > 1. Unless it can be justified as to why it is not relevant it may be necessary to carry out further assessment of the risk presented by the combination of actives.

The second instance is when the acute to chronic ratio (ACR) for a certain species is significantly higher than the average ratio of 10. In such a case, it might not be sufficient to refine the PNEC only for the species for which in Tier A a risk is identified. If it cannot be founded that the ACR is related to an effect in a specific taxonomic group, it may be necessary to test the chronic toxicity for those trophic levels for which these data are not available. Here, the relative sensitivity of the different taxonomic groups and the exposure levels should be taken into consideration.

2.6 Metabolites

In the last sentence of the 4th paragraph of the VICH guideline it is stated that "excreted metabolites representing 10% or more of the administrated dose and which do not form part of biochemical pathways should be added to the active substance to allow the PEC to be recalculated." In contrast to the definition in the glossary (active substances = parent and/or its metabolites) in this specific case the term active substance stands for the parent compound only.

2.7 Special Consideration for Biodegradation Data

As a general rule, the risk assessment in Tier A starts with a total residue approach, meaning that the PEC is based on the sum of the parent compound and all metabolites / degradation products. If a risk is identified based on this approach, refinement of the PEC should be considered based on data on metabolism and degradation in soil or manure. As stated in the previous section of the VICH guideline (§ 2.6) all metabolites can be subtracted from the total dose administered (i.e. 100%) if the amount excreted is less than 10% of the administered dose. There is one provision on the preceding discussion concerning the degradation of parent compound in soil or manure to degradation products, which are identical to metabolites. In this case it may be that the amount of metabolite plus the amount of its identical degradation product is more that 10% of the applied dose.

In the same section of the VICH guidance document, it is stated that for persistent compounds (e.g. DT90 > 1 year in soil based on an annual application) it may be necessary to recalculate the PEC initial; due to the possibility of accumulation in the environment as the application of manure in several successive years could lead to elevated concentrations of the active ingredient in soil. In these cases the PEC_{soil} at steady state can be calculated as follows:

$$PEC_{soil\,1year} = PEC_{soil\,initial} \times e^{\left(\frac{(-\ln 2 \times 365)}{DT_{50}}\right)}$$ Equation 4

$$Fs = \frac{\left(PEC_{soil\,initial} - PEC_{soil1year}\right)}{PEC_{soil\,initial}}$$ Equation 5

$$PEC_{soil\ plateau} = \frac{PEC_{soil\,initial}}{Fs}$$ Equation 6

where:

$PEC_{soil\ 1\ year}$ = Predicted Environmental Concentration in soil 1 year after spreading [$\mu g.kg^{-1}$]

$PEC_{soil\ initial}$ = Predicted Environmental Concentration in soil immediately after spreading [$\mu g.kg^{-1}$] (from Equation 1, Equation 2 or Equation 3)

DT_{50} = Half-life of active in soil [days]

Fs = Fraction degraded in soil one year after application

$PEC_{soil\ plateau}$ = Predicted Environmental Concentration in soil at plateau concentration [$\mu g.kg^{-1}$]

365 = Days per year [$day.yr^{-1}$]

3. Recommended Studies at Tier A and Tier B

3.1 Tier A Testing

3.1.1 Tier A Physical-Chemical Properties Studies

n-Octanol/Water Partition Coefficient

In the VICH guideline [3] the shake-flask method (OECD 107) or the HPLC method (OECD 117) is recommended. Some precautions for very lipophilic compounds, however, have to be taken as outlined in the Globally Harmonized System of Classification and Labelling of Chemicals.

"The shake-flask method is recommended when the log K_{ow} value falls within the range from –2 to 4. The shake-flask method applies only to essential pure substances soluble in water and n-octanol. For highly lipophilic substances, which slowly dissolve in water, data obtained by employing a slow-stirring method are generally more reliable. Furthermore, the experimental difficulties, associated with the formation of microdroplets during the shake-flask experiment, can to some degree be overcome by a slow-stirring method where water, octanol, and test compound are equilibrated in a gently stirred reactor. With the slow-stirring method (OECD 123) a precise and accurate determination of K_{ow} of compounds with log K_{ow} of up to 8.2 is allowed. As for the shake-flask method, the slow-stirring method applies only to essentially pure substances soluble in water and n-octanol. The HPLC method,

which is performed on analytical columns, is recommended when the log K_{ow} value falls within the range 0 to 6. The HPLC method is less sensitive to the presence of impurities in the test compound compared to the shake-flask method."

For more information see: http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html.

3.1.2 Tier A Environmental Fate Studies

Adsorption

An OECD guideline is available on the determination of the log K_{OC} by means of HPLC. However, this test method (OECD 121) should be used with care. Especially for polar compounds the method is not fully validated and might provide unreliable K_{OC} values. Also log K_{OC} values > 5.6 should not be considered to be reliable. For this reason the OECD 106 test method is recommended, especially for ionisable VMPs.

If OECD guideline 106 is followed then normally the average K_{OC} value of five soil types is used in the risk assessment. If fewer soil types are investigated then the lowest K_{OC} value is used.

Since veterinary drugs could be large molecules with several functional groups and a tendency to speciate into ionic species around environmental pH values, other soil components with polar and/or charged surfaces might also act as sorbents. Additionally, sorption behaviour is known to be strongly pH-dependent. If this type of behaviour is confirmed by further studies on the sorption behaviour of pharmaceuticals, models need to be adapted to allow accounting for additional sorbents and pH-dependence of sorption.

Photolysis

So far there is little evidence that for products used in terrestrial animals photolysis will play a significant role in the degradation of the active ingredient in the environment. It is expected that there will be little direct exposure of the active to light in the soil, manure or dung matrix. These conclusions were confirmed by Thiele-Bruhn [16], who concluded that under field conditions, photodecomposition is a negligible process for the detoxification of antibiotics. If the active ingredient is excreted in urine directly into water it is considered that the entry of the animals will cause sufficient turbidity so that photolysis will not play a significant role.

For products used in fish, which are added directly to the water, it is considered that photolysis may have a role in the degradation of the active ingredient. In this situation if the applicant considers it to be relevant the photolysis of the active ingredient can be determined by following the OECD guideline 316 on "Phototransformation of Chemicals in Water-Direct and Indirect Photolysis" [17].

Degradation in marine systems.

It may be appropriate to carry out the degradation study for the aquatic system under saltwater conditions. This is relevant when a VMP is used in aquaculture in the marine environment. It is recommended to follow the advice given in the guideline for new and existing substances (the EU Technical Guidance Document (TGD)) [18], which gives the following guidance.

As a general rule, degradation rates or half-lives determined in tests simulating the conditions in the actual aquatic environment under consideration should be used whenever available. However, expert judgement of the validity and quality of the test data is necessary. The origin (e.g. relevance of sampling site) of the sea water/sediment inoculum shall always be evaluated in connection with

assessment and use of simulation test results. Biotransformation (identification of metabolism pathways and major metabolites) and mineralisation data may be derived from one of the standardised simulation tests by using samples from the particular environment as inoculum. Standardised simulation test methods for various marine compartments are:

- *Aquatic (pelagic) compartment*: OECD 309 "Aerobic mineralisation in Surface Water - Simulation Biodegradation Test". (Adopted April 2004)
- *Aquatic (pelagic) compartment*: ISO/DIS 14592-1: "Evaluation of the aerobic biodegradability of organic compounds at low concentrations – Part 1" (published international standard 2002) (The ISO method has been the basis for above mentioned OECD test guideline)
- *Turbid aquatic/sediment dispersed compartment*: ISO/DIS 14592-2: "Evaluation of the aerobic biodegradability of organic compounds at low concentrations – Part 2" (published international standard 2002) and OECD 308: "Aerobic and anaerobic transformation in aquatic sediment systems " (aerobic test)
- *Anaerobic sediment compartment*: OECD 308 "Aerobic and anaerobic transformation in aquatic sediment systems" (strictly anaerobic test) (adopted April 2002)

3.1.3 Tier A Effects Testing

3.1.3.1 Tier A Aquatic Effect Studies

Table 3 of the VICH Phase II guideline gives the studies and assessment factors recommended in Tier A of the EIA which are to be used in the assessment of risk to aquatic organisms.

In a footnote under Table 3 it is stated, "For substances with anti-microbial activity, some regulatory authorities prefer a blue-green algae rather than a green algae species be tested". Indeed, several studies have demonstrated that blue-green algae (cyanobacteria) generally are more sensitive to anti-microbial agents than green algae [19-21] It is therefore preferred in the EU to use blue-green algae when testing the toxicity of active ingredients with anti-microbial properties.

As indicated in Table 3, for the salt-water compartment no internationally accepted, i.e. ISO or OECD, guidelines are currently available for testing effects on fish. Guidance may, however, be found in the guideline "Standard Guide for Conducting Acute Toxicity Tests on Test Materials with Fishes, Macroinvertebrates, and Amphibians" (E729-96 (2002)) available from the American Society for Testing of Materials (ASTM) [22], and the Office of Prevention, Pesticides and Toxic Substances (OPPTS) [23] guideline "Fish acute toxicity test, freshwater and marine" (850.1075) which can be downloaded from the web-page of the OPPTS [23], http://www.epa.gov/oppts/.

3.1.3.2 Tier A Terrestrial Effect Studies

Effects on collembola

The VICH guideline states, "For endo/ectoparasiticides used in intensively reared animals only, some regulatory authorities may seek additional information on the toxicity to non-target arthropods (e.g. Collembola)". The need for additional information is endorsed by the EU in order to assess the risk for terrestrial invertebrates.

No OECD guideline currently exists for a toxicity test with Collembola although one is under development. However, within the International Standard Organisation (ISO) an internationally accepted guideline exists [24]. This guideline should be followed when carrying out a Collembola test until an OECD guideline is approved.

As the ISO guideline is a chronic test, the PNEC for collembola is determined by applying an assessment factor of 10 to the NOEC.

Effects on dung organisms

During discussions of the VICH Ecotoxicity/Environmental Impact Assessment Expert Working Group it was noted that there are currently no internationally recognized guidelines for laboratory testing for effects of veterinary medicines on dung flies and dung beetles. Work therefore started to develop and ring-test toxicity test methods for dung beetles and dung flies by the Dung Organism Toxicity Testing Standardisation (DOTTS) initiative with members from the EU, North America, South Africa, and Asia/Pacific.

The aims of the group are as follows:

- Exchange of information about testing the effects of veterinary drugs on dung organisms
- Development of test protocols for toxicity testing with dung flies and dung beetles
- Performance of ring tests with dung flies and dung beetles in order to standardize and validate the test protocols

In December 2002 DOTTS became affiliated with SETAC Europe. As such, the group abides by the scientific principles of SETAC, and acts in the interests of government regulators, the veterinary pharmaceutical industry and research institutions (e.g. universities or contract laboratories). Recently, DOTTS provided a final draft of a test guideline with two species of dung flies [25], which probably will be finalised at the next meeting of the National Co-ordinators. In addition, an OECD draft guidance document on the testing of dung beetles has been compiled, which covers also two species [26]. Its finalisation will require approximately another year. Further recommendation and drafts of the test guidelines are given on the OECD website http://www.oecd.org/findDocument/0,2350,en_2649_34377_1_1_1_1_37465,00.html.

Assessment of the risk for insect eating birds

In the EU the exposure scenario where birds are exposed to active ingredient when feeding on insects on the backs of treated animals is considered to be minor. No assessment of the risk to birds from feeding on the backs of animals treated with parasiticides will be required for the EU.

3.1.4 Risk Assessment at Tier A

3.1.4.1 PEC refinement

In Phase II Tier A the PECs are initially calculated based on the total residue approach and compared with the PNEC derived from the base set of toxicity tests. If the RQ is above one, the adjustments presented below can be used to refine the PECs.

Depending upon the scenario and the characteristics of the active ingredient being studied, a number of options may be available to refine the exposure assessment. Broadly speaking, these refinements fall into one or more of the following categories:

- Refinement based on metabolism
- Refinement based on the excretion pattern
- Refinement based on degradation in manure/slurry
- Refinement based on degradation in soil

If the risk assessment is part of a centralised, decentralised or mutual recognition procedure the PEC refinement has to cover situations and agricultural practice representative for the whole of the EU region. This fact has implications on a number of default values like manure storage and number of spreading events per year.

When considering the suitability of refinement options it should be noted that, as a general principle, any departure from the default values provided in Chapter 5 must be fully justified and, if possible, supported by suitable evidence.

Refinement based on metabolism

The PEC_{soil} can be refined by determining the actual composition of the excreted residue. The VICH Phase II guideline suggests that metabolites representing less than 10% of the administered dose can be subtracted from the total dose administered. This procedure will result in the calculation of the fraction of the administered dose still considered to be active. The PEC_{soil} calculated in Phase I and used initially in Phase II Tier A can be refined as shown. It is known that bacteria are capable of converting the conjugated metabolites back to the original metabolite. It is very likely that this process continues after the manure is excreted. Therefore, all conjugated metabolites originating from the same Phase I metabolite should be summed and also this total amount should not be higher than 10% of the dose.

$$PEC_{soil\,refined} = PEC_{soil\,initial} \times Fa$$ Equation 7

where:

$PEC_{soil\ refined}$ = The refined Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$]

$PEC_{soil\ initial}$ = The initial Predicted Environmental Concentration in soil [$\mu g.kg^{-1}$] (from Equation 1, Equation 2 or Equation 3)

Fa = The fraction of the dose considered to be active [value between 0 and 1]

Refinement based on the excretion pattern

For ecto- and endo parasiticides applied to pasture animals, a reasonable maximum concentration in dung has to be derived, which preferably is determined in ADME-experiments. When this information is not available, a worst-case maximum is calculated using the equation shown below.

$$PEC_{dung} = \frac{D \times BW \times Fdh}{M_{dung}}$$ Equation 8

where:

PEC_{dung} = The Predicted Environmental Concentration in dung [$mg.kg_{wwt}^{-1}$]

D = Daily dose of the active ingredient [$mg.kg_{bw}^{-1}.d^{-1}$]

BW = Animal body weight [kg] (see Table 5)

Fdh = The highest fraction of the dose excreted in dung in 1 day, if there is no information on this the value is 1, i.e. all excretion occurs in 24 hours

M_{dung} = Mass of dung produced in one day [$kg.d^{-1}$] (see Table 5)

Table 5. Daily dung production for pasture animals

Animal type	Bodyweight (kg)	Daily dung production ($kg_{wwt}.d^{-1}$)
Dairy cow	600	36
Beef cattle	330	13
Ewe	80	2
Lamb	36	0.9
Horse	600	25
Pony	250	10
Goat	60	1.6
Red Deer (stag)	110	2.8

Dung production values are based on information provided in ASAE D384.1 of Dec 1993. American Society of Agricultural Engineers, St Joseph, Michigan, USA [27]

Refinement based on degradation in manure

At present no standard protocol for investigating degradation in manure/slurry is available. Such studies should always be performed under realistic worst-case storage conditions. Except for chicken manure, aerobic slurry studies are generally not considered representative for the storage condition of manure.

If degradation is to be considered in Phase II, the PEC_{manure} should be calculated for a storage time similar to one animal cycle and by doing so the amount of manure is also set equal to the amount produced in that storage period which fills the annual nitrogen quota of 170 kg $N.ha^{-1}$. It is also necessary to consider that the animals could be treated at any time during the period of housing and that if animals are treated at the beginning of the storage period there will be more time for the active

ingredient to degrade than if they were treated at the end of the storage period. For this reason the time for degradation of the active is taken to be half the storage time of the manure. (For simplicity it is assumed that if there are a number of daily treatments the interval between these is not considered in the calculation).

To calculate the PEC_{soil} by taking into account the degradation during storage the following the equations can be used:

$$Mi = D \times Ad \times BW \times Fh$$ Equation 9

$$Mt = Mi \times e^{\left(\frac{\left(-\ln(2)\times\left(Tst/2\right)\right)}{DT_{50}}\right)}$$ Equation 10

$$PEC_{soil\ refined} = \left(\frac{Mt \times 170}{1500 \times 10000 \times 0.05 \times Ns}\right) \times 1000$$ Equation 11

where:

$PEC_{soil\ refined}$ = The refined Predicted Environmental Concentration in soil [µg.kg^{-1}]

Mi = Mass of active in manure/slurry [mg]

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 6).

Fh = Fraction of the herd treated [value between 0 and 1] (see Table 2)

Tst = Length of time manure is stored [days] (see Table 6).

DT_{50} = Half-life of active in manure [days]

Mt = Mass of active in manure/slurry after the mean storage time [mg]

170 = EU nitrogen spreading limit [kg.N.ha^{-1}]

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]

Ns = Nitrogen produced during storage time [kgN]

1000 = Conversion factor [1000 µg.mg^{-1}]

Table 6. Default values for use in calculating the $PEC_{soil\ refined}$ following degradation in manure.

Animal type	Number of animals raised per place per year	Bodyweight (kg)	Nitrogen produced during storage time (kg)	Storage time (days)*
Calf	1.8	140	2.5	91
Dairy cow	1	425	15	91
Cattle (0-1 year)	1	200	4.3	91
Cattle (>2 years)	1	450	8.8	91
Weaner pig (to 25 kg)	6.9	12.5	0.33	53
Fattening pig (25-125 kg)	3	65	1.9	91
Sow (with litter)	1	240	6.5	91
Broiler	9	1	0.03	41
Laying hen	1	1.6	0.09	91
Replacement layer	2.6	0.8	0.06	91
Broiler breeder	1	1.7	0.17	91
Turkey	2.7	6.5	0.23	91
Duck	7	1.6	0.06	52
Horse	1	400	8.8	91
Rabbit	8	1.4	0.044	46

* When the number of cycles is 4 or less, the storage time is set equal to 3 months based on data from reference 11.

Refinement based on degradation in soil

Calculating a PEC based on a time-weighted average or after a certain time period should not be considered. Unless it can be shown otherwise it is anticipated that the degradation rate in the soil after manure application equals the degradation rate in the laboratory toxicity tests. This means that nominal effects concentrations should be compared to peak PEC concentrations and the time weighted average must only be compared to effects concentrations derived from measured values.

Refinement of PEC soil based on soil degradation data is possible when it is realistic to assume that manure is spread in more than one spreading event. In that case the concentration calculated after the last spreading event should be taken.

In the case of arable land, manure/slurry is usually applied to fulfil the permissible limit during a single, annual application event. This partly reflects the fact that the presence of a crop will prevent applications of manure/slurry throughout much of the year.

In the case of grassland, it is more typical to make a number of applications of manure/slurry throughout the year, with the total amount of nitrogen applied adding up to equal the annual permissible limit. It is up to the applicant to provide information to support the number of spreading events, which have been taken to occur on grassland.

The following formula can be used to calculate the $PECsoil_{refined}$ after the last spreading event:

$$PECsoil_{refined} = PECsoil_{single\ event} \cdot \frac{1-Frs^{Nspreading}}{1-Frs}$$ Equation 12

where $PECsoil_{single\ event}$ is given by:

$$PECsoil_{single\ event} = \frac{PECsoil_{initial}}{N_{spreading}}$$ Equation 13

$PECsoil_{initial}$ is the outcome of eq. 1.
$PEC_{soil\ single\ event}$ is the concentration in soil obtained after one grassland manure application. Like $PEC_{soil\ initial}$ (eq. 1), $PEC_{soil\ single\ event}$ is also an 'initial' concentration, which means that no degradation has been taken into account in those PEC_{soil} values.

$$Frs = e^{-k \cdot Tinterval\ spreading}$$ Equation 14

$$k = \frac{\ln 2}{DT_{50}}$$ Equation 15

where:

$PEC_{soil\ refined}$ = The refined Predicted Environmental Concentration in soil after last spreading event [$\mu g.kg^{-1}$]

$PEC_{soil\ single\text{-}event}$ = The Predicted Environmental Concentration in soil immediately after spreading [$\mu g.kg^{-1}$]

*F*rs = Fraction remaining in soil after time $T_{interval\ spreading}$

Nspreading = number of spreading events

Tinterval spreading = Time between spreading events [days]

DT_{50} = Half-life of active in soil [days]

k = rate constant

3.2 Criteria for Tier B Testing

In the VICH guideline it is stated that if the RQ for aquatic invertebrates is ≥1 then the $PEC_{sediment}/PNEC_{sediment}$ ratio has to be considered. When a risk for sediment dwelling organisms is identified then testing of sediment organisms is needed. For substances with a log K_{ow} ≥5, the RQ has to be <0.1 when based on equilibrium partitioning in order to take into account the possible uptake via ingestion of sediment. The equilibrium partitioning is based on the following equation:

$$PNEC_{sediment} = \frac{K_{sed-water}}{RHO_{sed}} \times PNEC_{surface\ water} \times 1000 \times CONV_{sed}$$ Equation 16

$$K_{sed-water} = Fwater_{sed} + \left(Fsolid_{sed} \times \frac{Kp_{sed}}{1000} \times RHO_{solid} \right)$$ Equation 17

$$CONV_{sed} = \frac{RHO_{sed}}{Fsolid_{sed} \cdot RHO_{solid}}$$ Equation 18

$$Kp_{sed} = Foc_{sediment} \times K_{oc}$$ Equation 19

where:

$PNEC_{sediment,}$ = Predicted No Effect Concentration for sediment-dwelling organisms [$\mu g.kg_{dwt}^{-1}$]

$CONV_{sed}$ = Conversion factor for sediment concentrations: wwt to dwt [$kg_{wwt}.kg_{dwt}^{-1}$] (equal to 2.6)

$PNEC_{surfacewater}$ = Predicted No Effect Concentration for aquatic organisms [$\mu g.l^{-1}$]

$K_{sed-water}$ = Sediment-water partition coefficient [$m^3.m^{-3}$]

RHO_{sed} = Bulk density of sediment [1300 $kg_{wwt}.m^{-3}$]

RHO_{solid} = Bulk density of solids [2500 $kg_{dwt}.m^{-3}$]

$Fwater_{sed}$ = Volume fraction of water in sediment [0.8 $m^3.m^{-3}$]

$Fsolid_{sed}$ = Volume Fraction of solids in sediment [0.2 $m^3.m^{-3}$]

Kp_{sed} = Partition coefficient solids and water in sediment (v/w) [$l.kg^{-1}$]

K_{oc} = Organic carbon partition coefficient [$l.kg^{-1}$]

$Foc_{sediment}$ = Weight fraction organic carbon in sediment [0.05 $kg.kg^{-1}$]

1000 = Conversion for litre to m^3 [$l.m^{-3}$]

If the $PNEC_{sediment}$ has to be expressed on a wet weight basis the expression $CONV_{sed}$ is omitted from Equation 16.

The composition of the sediment used for the tests should depend on the requirements of the test species and should therefore be gathered as described in the respective test methods. The use of artificial sediment is recommended. However, if there is experience with special natural sediments, these can also be used for the test as long as the properties of the sediment are described in detail.

The organic carbon content of the sediment may influence the bioavailability and therefore the toxicity of the test substance. Therefore, for comparison of sediment tests, the organic carbon content of the test sediment should be within a certain range. The OECD guideline 218 for the test with *Chironomus* using spiked sediment recommends an organic carbon content of the test sediment of 2 % (+/- 0.5 %).

Various techniques can be used to spike sediments, e.g. wet spiking and dry spiking. A flexible approach should be adopted due to variations in physico-chemical properties of test substances. However, it has to be guaranteed that the substance will not desorb from the sediment particles during the test as this would lead to an underestimation of the toxicity. To limit such desorption an adequate equilibration period before the start of the test is recommended. In addition the actual concentration of the test substance in the sediment should be monitored at least at the beginning and at the end of the test to check the efficiency of the spiking technique and the stability of the test substance concentration.

3.3 Tier B Testing

3.3.2 Tier B Environmental Fate Studies

In the VICH guideline it is stated that if the log K_{ow} is ≥4, evidence from absorption, distribution, metabolism and excretion (ADME) and biodegradation studies and molecular mass should be considered to see whether there is the potential for bioaccumulation to occur. If so, then a bioconcentration factor (BCF) study is recommended to be carried out at Tier B. Evidence of bioaccumulation from ADME studies would be the presence of high concentrations of the active in fat compared to other tissues and/or the slow depletion of the residue from fat tissue. In view of the fact that in general the activity of enzymes involved in the transformation of xenobiotics decrease at lower trophic levels, the lack of accumulation in mammals does not automatically exclude the potential for accumulation in fish.

Guidance on the risk assessment of secondary poisoning

General approach

To assess the risk for secondary poisoning, the use of a predicted BCF based on quantitative structure activity relationships (QSARs) may be considered. The following guidance on the use of QSARs and how to determine the risk for secondary poisoning (when the BCF is above the trigger value) is taken from the EU TGD for new and existing substances [18] with some modification to make it applicable for the risk assessment of VMPs. All references given in this section can be found in the relevant section in Chapter 2 of the aforementioned EU guidance.

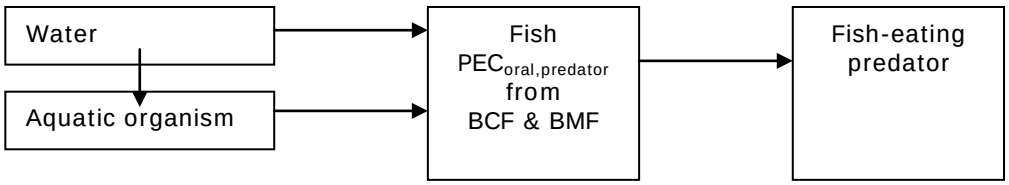
Assessment of the potential impact of substances on top predators is based on the accumulation of hydrophobic chemicals through the food chains, which may follow many different pathways along different trophic levels. This accumulation may result in toxic concentrations in predatory birds or mammals ingesting biota containing the chemical. This effect is called secondary poisoning and should, in principle, be assessed by comparing the measured or estimated concentrations in the tissues and

organs of the top predators with the no-effect concentrations for these predators expressed as the internal dose. In practice, however, data on internal concentrations in wild animals are hardly ever available and most no-effect levels are expressed in term of concentrations of the food that the organisms consume (i.e. in $mg.kg^{-1}$ food). Therefore, the actual assessment (see below) is normally based on a comparison of the (predicted) concentration in the food of the top predator and the (predicted) no-effect concentration, which is based on studies with laboratory animals. A distinction is made between the methodology used to assess the effects of substances whose effects can be related directly to bioconcentration (direct uptake via water) and those where also indirect uptake via the food may contribute significantly to the bioaccumulation. Bioaccumulation of metallic species is not considered explicitly in this section.

For substances with a log Kow < 5 the primary uptake route is direct uptake from the water phase. In the absence of data on other uptake routes, it is assumed that the direct uptake accounts for 100% of the intake. For substances with a log Kow ≥ 5, other uptake routes such as intake of contaminated food or sediment may become increasingly important. In particular the uptake through the food chains eventually leading to secondary poisoning should be considered. A strategy for the assessment of secondary poisoning has been developed. This strategy takes account of the $PEC_{aquatic}$, the direct uptake and resulting concentration in food of aquatic organisms and the mammalian and avian toxicity of the chemical. On this basis, possible effects are estimated on birds and mammals in the environment via uptake through the food-chain water → aquatic organisms → fish → fish-eating mammal or fish-eating bird Romijn et al (1993).

A schematic view of the assessment scheme for the exposure route water → aquatic organisms → fish → fish-eating mammal or fish-eating bird described above is given in Figure 1.

Figure 1. Assessment of secondary poisoning



No specific assessment of the risk to fish as a result of the combined intake of contaminants from water and contaminated food (aquatic organism) is considered necessary as this is assumed to be covered by the aquatic risk assessment and the risk assessment for secondary poisoning of fish-eating predators.

The risk to the fish-eating predators (mammals and/or birds) is calculated as the ratio between the concentration in their food ($PEC_{oral,\ predator}$) and the no-effect-concentration for oral intake ($PNEC_{oral}$). The concentration in fish is a result of uptake from the aqueous phase and intake of contaminated food (aquatic organisms). Thus, $PEC_{oral,\ predator}$ is calculated from the bioconcentration factor (BCF) and a biomagnification factor (BMF). Note that $PEC_{oral,\ predator}$ could also be calculated for other relevant species that are part of the food of predators. The details of the individual assessment steps are described in the following sections.

Calculation of BCF from log Kow

If measured BCF values are not available, the BCF for fish can be predicted from the relationship between Kow and BCF. Various methods are available to calculate Kow. Often a large variation is found

in the Kow values of a chemical by using different methods. Therefore the Kow value must have been evaluated by an expert

For substances with a log Kow of 2-6 the following linear relationship can be used as developed by Veith et al. (1979).

$$\log BCF_{fish} = 0.85 \cdot \log Kow - 0.70$$ Equation 20

For substances with a log Kow higher than 6 a parabolic equation can be used.

$$\log BCF_{fish} = -0.20 \cdot logKow^2 + 2.74 \cdot \log Kow - 4.72$$ Equation 21

where:

Kow = Octanol-water partition coefficient

BCF_{fish} = Bioconcentration factor for fish on wet weight basis [$l.kg_{wet\ fish}$]

It should be noted that due to experimental difficulties in determining BCF values for such substances this mathematical relationship has a higher degree of uncertainty than the linear one. Both relationships apply to compounds with a molecular weight of less than 700. For chemicals with a molecular weight of more than 700 g/mol, the BCF tends to decrease but where there is lack of experimental data, the QSAR can be used as an initial worst-case estimate.

Calculation of a predicted environmental concentration in food

The concentration of contaminant in food (fish) of fish-eating predators ($PEC_{oral,\ predator}$) is calculated from the PEC for surface water, the measured or estimated BCF for fish and the biomagnification factor (BMF):

$$PEC_{oral,predator} = PEC_{water} \cdot BCF_{fish} \cdot BMF$$ Equation 22

where:

$PEC_{oral,\ predator}$ = Predicted Environmental Concentration in food[$mg.kg_{wet\ fish}^{-1}$]

PEC_{water} = Predicted Environmental Concentration in water[$mg.l^{-1}$]

BCF_{fish} = Bioconcentration factor for fish on wet weight basis[$l.kg_{wet\ fish}^{-1}$]

BMF = Biomagnification factor in fish

The biomagnification factor (BMF) is defined as the relative concentration in a predatory animal compared to the concentration in its prey ($C_{predator}/C_{prey}$). The concentrations used to derive and report BMF values should, where possible, be lipid normalised.

An appropriate PEC_{water} reflecting the foraging area of fish-eating mammals and birds should be used for the estimate. The foraging area will of course differ between different predators, which makes it difficult to decide on an appropriate scale. As a worst case it can be assumed that 100% comes from the local area (represented by the annual average PEC for the local scale). As a refinement a scenario can be considered where 50% of the diet comes from a local area and 50% of the diet comes from a regional area.

The BMF should ideally be based on measured data. However, the availability of such data is at present very limited and therefore, the default values given in Table 7 should be used. By establishing these factors it is assumed that a relationship exists between the BMF, the BCF and the log Kow. When measured BCF values are available, these should form the basis for deciding on the size of the BMF.

Table 7. Default BMF values for organic substances

Log Kow of substance	BCF (fish)	BMF
<4.5	< 2,000	1
4.5 - <5	2,000-5,000	2
5 – 8	> 5,000	10
>8 – 9	2,000-5,000	3
>9	< 2,000	1

Calculation of the predicted no-effect concentration ($PNEC_{oral}$)

Only toxicity studies reporting on dietary and oral exposure are relevant as the pathway for secondary poisoning is referring exclusively to the uptake through the food chain. Secondary poisoning effects on bird and mammal populations rarely become manifest in short-term studies. Therefore, results from long-term studies are strongly preferred, such as NOECs for mortality, reproduction or growth. If no adequate toxicity data for mammals or birds are available, an assessment of secondary poisoning cannot be made.

For some VMPs, toxicity data for birds (e.g. OECD 205 (LC50, 5-day acute avian dietary study) or OECD 206 (chronic study)) may be present. In the absence of any avian toxicity studies, the results of mammalian repeated-dose toxicity tests are used to assess secondary poisoning effects. Extrapolation from such test results gives a predicted no-effect concentration in food ($PNEC_{oral}$) that should be protective to other mammalian and avian species.

Acute lethal doses LD_{50} (rat, bird) are not acceptable for extrapolation to chronic toxicity, as these are not dietary tests. Acute effect concentrations (e.g. OECD 205) for birds are acceptable for extrapolation. The results of the available mammalian or avian tests may be expressed as a concentration in the food ($mg.kg_{food}^{-1}$) or a dose (mg.kg body weight.day^{-1}) causing no effect. For the assessment of secondary poisoning, the results always have to be expressed as the concentration in food. When toxicity data are given as NOAEL only, these NOAELs can be converted to NOECs with the following two formulae:

$$NOEC_{bird} = NOAEL_{bird} \cdot CONV_{bird}$$ Equation 23

$$NOEC_{mammal,food_chr} = NOAEL_{mammal,oral_chr} \cdot CONV_{mammal}$$ Equation 24

where:

$NOEC_{bird}$	=	NOEC for birds ($kg.kg_{food}^{-1}$)
$NOEC_{mammal,\ food\ chr}$	=	NOEC for mammals ($kg.kg_{food}^{-1}$)
$NOAEL_{bird}$	=	NOAEL for birds (kg.kg bw·d^{-1})
$NOAEL_{mammal,\ oral\ chr}$	=	NOAEL for mammals (kg.kg bw·d^{-1})
$CONV_{bird}$	=	Conversion factor from NOAEL to NOEC (kg bw·d·kg_{food}^{-1})

$CONV_{mammal}$ = Conversion factor from NOAEL to NOEC (kg bw·d·kg_{food}^{-1})

Conversion factors for laboratory animals are presented in Table 8.

Table 8. Conversion factors from NOAEL to NOEC for several mammalian and one bird species.

Species	**Conversion factor (bw/dfi*)**
Canis domesticus	40
Macaca sp.	20
Microtus spp.	8.3
Mus musculus	8.3
Oryctolagus cuniculus	33.3
Rattus norvegicus (> 6 weeks)	20
Rattus norvegicus (≤ 6 weeks)	10
Gallus domesticus	8

* bw = body weight (g); dfi = daily food intake (g/day)

NOECs converted from NOAELs have the same priority as direct NOECs.

The $PNEC_{oral}$ is ultimately derived from the toxicity data (food basis) applying an assessment factor. In formula:

$$PNEC_{oral} = \frac{TOX_{oral}}{AF_{oral}}$$ Equation 25

where:

$PNEC_{oral}$ = PNEC for secondary poisoning of birds and mammals[$kg.kg_{food}^{-1}$]
AF_{oral} = Assessment factor applied in extrapolation of PNEC
TOX_{oral} = Either $LC50_{bird}$, $NOEC_{bird}$ or $NOEC_{mammal, food, chr}$ [$kg.kg_{food}^{-1}$]

The assessment factor (AF_{oral}) takes into account interspecies variation, acute/subchronic to chronic extrapolation and laboratory data to field impact extrapolation. Some specific considerations need to be made for the use of the assessment factor for predators.

A report from the Canadian Council of Ministers of the Environment contains wildlife data on body weight and daily food ingestion rates for 27 bird and 10 mammalian species. In addition, Schudoma et al. (1999) derived the mean body weight and daily food intake for the otter. The currently available set on wildlife bw/dfi ratios ranges from 1.1 to 9 for birds and from 3.9 to 10 for mammalian species. Comparison of these wildlife conversion factors with the values given in Table 8 for laboratory species (8.3 to 40) shows that the wildlife species often have a lower bw/dfi ratio than laboratory animals. The difference can be up to a factor of 8 for birds and 10 for mammals. This difference is in theory accounted for in the use of the interspecies variation factor that is part of the standard assessment factor. The interspecies variation, however, should comprise more than just the bw/dfi differences between species, e.g. the differences in intrinsic sensitivity. The protective value of the "normal" interspecies variation factor may therefore be questionable in the case of predators. On top of that, many predator species are characterised by typical metabolic stages in their life-cycle that could make

them extra sensitive to contaminants in comparison with laboratory animals (e.g. hibernation or migration). Similar to the bw/dfi differences, this aspect goes beyond the "normal" interspecies variation.

The AF_{oral} should compensate for the above-mentioned specific aspects in the effects assessment of predators. A factor of 30, accounting for both interspecies variation and lab-to-field extrapolation, is considered to be appropriate for this purpose. In addition, acute/subchronic to chronic needs to be taken into account. The resulting assessment factors are given in Table 9.

Table 9. Assessment factors for extrapolation of mammalian and bird toxicity data.

TOX_{oral}	**Duration of test**	**AF_{oral}**
$LC50_{bird}$	5 days	3,000
$NOEC_{bird}$	chronic	30
$NOEC_{mammal,\ food,chr}$	28 days 90 days chronic	300 90 30

If a NOEC for both birds and mammals is given, the lower of the resulting PNECs is used in the risk assessment.

Assessment of secondary poisoning via the aquatic food chain

The risk for fish-eating birds is determined by dividing the $PEC_{oral,\ predator}$ by the $PNEC_{oral}$. When the ratio is > 1 there is a potential risk of secondary poisoning. In such case it may be necessary to conduct additional laboratory tests (e.g. tests of bioaccumulation in fish or feeding studies with laboratory mammals or birds) in order to obtain better data.

It should be recognised that the schematic aquatic food chain water → aquatic organism → fish → fish-eating bird or mammal is a very simplistic scenario as is the assessment of risks for secondary poisoning based on it. Any other information that may improve the input data or the assessment should therefore be considered.

The simplified food chain is only one example of a secondary poisoning pathway. Safe levels for fish-eating animals do not exclude risks for other birds or mammals feeding on other aquatic organisms (e.g. mussels and worms). Therefore it is emphasised that the proposed methodology gives only an indication that secondary poisoning is a critical process in the aquatic risk characterisation of a chemical.

For a more detailed analysis of secondary poisoning, several factors have to be taken into account including:

- Differences in metabolic rates between animals in the laboratory and animals in the field;
- Normal versus extreme environmental conditions: differences in metabolic rate under normal field conditions and more extreme ones, e.g. breeding period, migration, winter;
- Differences in caloric content of different types of food: cereals versus fish, worms or mussels. As the caloric content of fish is lower than cereals birds or mammals in the field must consume more fish compared to cereals for the same amount of energy needed leading to a higher body burden of the test compound;
- Test compound assimilation efficiency: differences in bioavailability in test animals (surface application of a test compound) and in the field (compound incorporated in food) and/or;

- Relative sensitivity of animals for certain chemicals: differences in biotransformation of certain compounds between taxonomic groups of birds or mammals. The US EPA uses a species sensitivity factor (SSF), which ranges from 1 to 0.01.

Whether these factors should be used is still under debate.

Assessment of secondary poisoning via the terrestrial food chain

Biomagnification may also occur via the terrestrial food chain. A similar approach as for the aquatic route can be used here. The food-chain soil → earthworm → worm-eating birds or mammals are used as has been described by Romijn et al. (1994). The $PNEC_{oral}$ is derived in the same way as for the aquatic route. Since birds and mammals consume worms with their gut contents and the gut of earthworms can contain substantial amounts of soil, the exposure of the predators may be affected by the amount of substance that is in this soil. The $PEC_{oral,\ predator}$ is calculated as:

$$PEC_{oral,\ predator} = C_{earthworm}$$ Equation 26

Where $C_{earthworm}$ is the total concentration of the substance in the worm as a result of bioaccumulation in worm tissues and the adsorption of the substance to the soil present in the gut.

For PEC_{soil} the concentration is averaged over a period of 180 days. The method of calculating the time weighted average PEC_{soil} can be found in the EU TGD [18], Chapter 2, section 2.3.8.5. The same scenario is used as for the aquatic food chain (see above), i.e. as a worst case it can be assumed that 100% comes from local area.

Gut loading of earthworms depends heavily on soil conditions and available food (lower when high quality food like dung is available). Reported values range from 2 to 20 % (kg dw gut.kg ww^{-1} voided worm), 10% can therefore be taken as a reasonable value. The total concentration in a full worm can be calculated as the weighted average of the worm's tissues (through BCF and pore water) and gut contents (through soil concentration):

$$C_{earthworm} = \frac{BCF_{earthworm} \cdot C_{porewater} \cdot W_{earthworm} + C_{soil} \cdot W_{gut}}{W_{earthworm} + W_{gut}}$$ Equation 27

where:

$PEC_{oral,\ predator}$ = Predicted Environmental Concentration in food [$mg.kg_{wet\ earthworm}^{-1}$]

$BCF_{earthworm}$ = Bioconcentration factor for earthworms on wet weight basis [$l.kg_{wet\ earthworm}^{-1}$]

$C_{earthworm}$ = Concentration in earthworm on wet weight basis [$mg.kg_{wet\ earthworm}^{-1}$]

$C_{porewater}$ = Concentration in pore water [$mg \cdot l^{-1}$]

C_{soil} = Concentration in soil [$mg.kg_{wwt}^{-1}$]

$W_{earthworm}$ = Weight of earthworm tissue [$kg_{wwt\ tissue}$]

W_{gut} = Weight of gut content [kg_{wwt}]

The weight of the gut contents can be rewritten using the fraction of gut contents in the total worm:

$$W_{gut} = W_{earthworm} \cdot F_{gut} \cdot CONV_{soil}$$ Equation 28

$$CONV_{soil} = \frac{RHO_{soil}}{F_{solid} \cdot RHO_{solid}}$$ Equation 29

where:

$CONV_{soil}$ = Conversion factor for soil concentration wet-dry weight soil [$kg_{wwt}.kg_{dwt}^{-1}$]

F_{solid} = Volume fraction of solids in soil [0.6 $m^3.m^{-3}$]

F_{gut} = Fraction of gut loading in worm [0.1 $kg_{dwt}.kg_{wwt}^{-1}$]

RHO_{soil} = Bulk density of wet soil [1700 $kg_{wwt}.m^{-3}$]

RHO_{solid} = Density of solid phase [2500 $kg_{dwt}.m^{-3}$]

$W_{earthworm}$ = Weight of earthworm tissue [$kg_{wwt\ tissue}$]

W_{gut} = Weight of gut content [kg_{wwt}]

Using this equation, the concentration in a full worm can be written as:

$$C_{earthworm} = \frac{BCF_{earthworm} \cdot C_{porewater} + C_{soil} \cdot F_{gut} \cdot CONV_{soil}}{1 + F_{gut} \cdot CONV_{soil}}$$ Equation 30

When measured data on bioconcentration in worms are available the BCF factors can be inserted in the above equation. For most substances, however, these data will not be present and BCF will have to be estimated. For organic chemicals, the main route of uptake into earthworms will be via the interstitial water. Bioconcentration can be described as a hydrophobic partitioning between the pore water and the phases inside the organism and can be modelled according to the following equation as described by Jager (1998):

$$BCF_{earthworm} = \frac{(0.84 + 0.012K_{ow})}{RHO_{earthworm}}$$ Equation 31

where for $RHO_{earthworm}$ by default a value of 1 ($kg_{wwt} \cdot l^{-1}$) can be assumed.

Jager (1998) demonstrated that this approach performed very well in describing uptake in experiments with earthworms kept in water. For soil exposure, the scatter is larger and the experimental BCFs are generally somewhat lower than the predictions by the model. The reasons for this discrepancy are unclear but may include experimental difficulties (a lack of equilibrium or purging method) or an underestimated sorption.[8]

Earthworms are also able to take up chemicals from food and it has been hypothesized that this process may affect accumulation at log Kow > 5 Belfroid *et al.* (1995). The data collected by Jager (1998) however, do not indicate that this exposure route actually leads to higher body residues than expected on the basis of simple partitioning. Care must be taken in situations where the food of

[8] According to certain studies some soil ingesting organisms may accumulate chemical substances not only from the soil pore water but also directly (possibly by extraction in the digestive tract) from the fraction of the substance adsorbed onto soil particles. This may become important for strongly adsorbing chemicals, e.g. those with a logKow > 3. For these compounds the total uptake may be underestimated. In other studies however it has been shown that soil digesters virtually only bioaccumulate the substance via the pore water, i.e. bioconcentrate chemical substances from the soil pore water. At present the latter process can be modelled by use of the equilibrium partitioning theory

earthworms is specifically contaminated (e.g. in case of high concentrations in leaf litter) although reliable models to estimate this route are currently lacking. The model was supported by data with neutral organic chemicals in soil within the range log Kow 3-8 and in water-only experiments from 1 to 6. An application range of 1 to 8 is advised and it is reasonable to assume that extrapolation to lower Kow values is possible. The model could also be used for chlorophenols when the fraction in the neutral form was at least 5% and when both sorption and BCF are derived from the Kow of the neutral species. The underlying data are however too limited to propose this approach in general for ionised chemicals.

The risk for worm-eating birds/mammals is determined by dividing the $C_{earthworm}$ by the $PNEC_{oral}$. When the ratio is > 1 there is a potential risk of secondary poisoning. In such case it may be necessary to conduct additional laboratory tests (e.g. tests of bioaccumulation in earthworm or feeding studies with laboratory mammals or birds) in order to obtain better data.

3.3.3 Tier B Environmental Effects Studies

3.3.3.1 Tier B Aquatic effects testing

Table 7 of the VICH Phase II guideline gives the studies and assessment factors recommended in Tier B of the EIA of the aquatic branch.

For the salt-water compartment no internationally accepted, i.e. ISO or OECD, guidelines are available. However, there are relevant guidelines available from the American Society for Testing of Materials (ASTM) for toxicity in salt water systems, which could be helpful in the context of selecting relevant salt-water studies for the Phase II, Tier B assessment. These include:

- E1191-03a Standard Guide for Conducting Life-Cycle Toxicity Tests with Saltwater Mysids
- E1367-03e1 Standard Test Method for Measuring the Toxicity of Sediment-Associated Contaminants with Estuarine and Marine Invertebrates.
- E1611-00 Standard Guide for Conducting Sediment Toxicity Tests with Marine and Estuarine Polychaetous Annelids.
- E2317-04 Standard Guide for Conducting Renewal Microplate-Based Life-Cycle Toxicity Tests with a Marine Meiobenthic Copepod.

An updated lists of active and historically ASTM guidelines and information on how to purchase these can be obtained from the web page of the American Society for Testing of Materials – www.astm.org.

The US EPA also publishes a number of useful harmonised guidelines for assessing environmental effects, including salt-water tests. These can be found and freely downloaded from the web-page of the Office of Prevention, Pesticides and Toxic Substances (OPPTS). Harmonised guideline within Series 850 (Ecological Effect Test Guidelines) can be found at www.epa.gov\oppts.

It is recommended that the national authorities be consulted before selecting and conducting an ecotoxicity test based on test methods not developed by OECD or ISO.

3.3.3.2 Tier B Terrestrial effect studies

No further guidance on Tier B testing is provided. However, if after Tier B testing the RQ still is above one, more studies may be needed in order to further elucidate the effects on terrestrial ecosystems.

Basically three different strategies for testing could be used.

1. To test more species in standard laboratory studies.
2. To test the toxicity of substances in the laboratory using more complex multi-species test systems or mesocosms.
3. To investigate the effects in field studies.

Strategy 1.

Generally very few additional international standard tests for single species are available for the terrestrial compartment other than the ones already mentioned in the previous sections.

For evaluating the chronic effects of substances on higher plants an ISO test guideline is available: ISO 22030:2005 Soil quality- Biological methods - Chronic toxicity in higher plants.

The American Society for Testing of Materials (ASTM) offers a test guideline for evaluating the effects of substances on nematodes in soil: E2172-01 Standard Guide for Conducting Laboratory Soil Toxicity Tests with the nematode *Caenorhabditis elegans.*

Strategy 2.

Various options may be available for using larger mesocosm or multi-species test systems. However, none of these are currently standardised to the extent that they have been accepted by OECD or ISO. The American Society for Testing of Materials (ASTM) offers a test guideline for evaluating the effects of substances in a soil core system:

- E1197-87 (2004) Standard Guide for Conducting a Terrestrial Soil-Core Microcosm Test.

The US EPA, Office of Prevention, Pesticides and Toxic Substances (OPPTS) also provide a useful test for terrestrial soil core system:

- OPPTS 850.2450 Terrestrial (Soil-Core) Microcosm test.

Furthermore, description of non-standarsised multi-species test systems can be found in the open literature. For example a special issue of the Journal *Ecotoxicology* (Vol 13, Issue 1-2, 2004) is devoted to the use of Terrestrial Model Ecosystems (TME) in terrestrial ecotoxicology.

Strategy 3.

To conduct and evaluate a field study is not always straightforward. They may be costly and laborious. Therefore detailed negotiation and discussion with authorities and experts is recommended before initiating such a study.

A number of considerations have to be made in the planning phase of a successful field study. These include (but are not limited to):

- Identify the targets of concern and the species to monitor
- Elucidate the natural temporal and geographically variation before initiating a field study.

- Use statistical (power) analyses to determine the minimum number of samples or replicates needed to demonstrate the decided difference, e.g. 25% change
- A number of confounding parameters need to be characterised both at the reference and the test site, e.g. sediment type, water flow, nutrient- and OM level and presence of other contaminants.
- A randomised block design can minimise the effects of confounding factors

Guidelines, which describe various steps in conducting terrestrial monitoring or studies in the field, are available from, e.g. The International Standard Organisation (ISO), The American Society for Testing of Materials (ASTM) and the US EPA, Office of Prevention, Pesticides and Toxic Substances (OPPTS). These may, some way or the other, also be useful for higher Tier assessment of VMPs and include:

- ISO 11268-3:1999. Soil quality -- Effects of pollutants on earthworms -- Part 3: Guidance on the determination of effects in field situations.
- ISO 16133:2004. Soil quality -- Guidance on the establishment and maintenance of monitoring programmes.
- ASTM: E1923-97 (2003) Standard Guide for Sampling Terrestrial and Wetlands Vegetation.
- OPPTS: 850.2500 Field-testing for terrestrial wildlife.
- OPPTS: 850.4300 Terrestrial plants field study.

Study design

When designing the field study it is important to select the optimal size of plot or study area for evaluating the effects on the species of concern. For example small plots may be sufficient if investigating the effects of anti-bacterial substances on essential microbial processes in soil, whereas larger plots are needed if the endpoint is long-term changes in earthworm populations. Small plots of least 10 m x 10 m are suitable for most circumstances and can be sited within an area of one hectare. The use of barriers will limit the re-invasion of plots from surrounding areas by epigeal fauna. Sites treated with insecticides or molluscicides in the previous year should be avoided.

Size of populations will vary according to the time of year and therefore field studies should generally be conducted when numbers of species and individuals are high provided that this is also the relevant time of year regarding use and spreading of the VMP.

Treatment of plots should be at the maximum rate of disposal to land. A toxic standard, e.g. propetamphos or benomyl, should be included in order to confirm the ability of the trial design to detect effects. Untreated controls, e.g. with no fertiliser, with inorganic fertiliser and/or manure from non-medicated animals, are also needed to measure natural fluctuations in populations during the trial.

Interpretation of data should take into account the range of species affected as well as the magnitude and duration of effect. Some guidance on interpreting and evaluating results from field studies may be found on the website of the International Organisation for Biological Control (IOBC) (www.iobc-wprs.org).

4. Aquaculture branch

As stated in the Phase II guidance aquaculture practices may vary widely between VICH regions. It is also true that aquaculture can vary widely between and within EU Member States. In addition the number of pharmaceuticals developed and authorised for use in aquaculture in Europe is small and applications for new authorisations are rare. For this reason the CVMP following recommendations from

its Environmental Risk Assessment Working Party has decided at this time not to provide any additional guidance on the Phase II assessment of products intended for use in aquaculture.

In the EU Member States the largest aquaculture industry is that represented by farmed salmon found in Scotland. In this industry salmon are kept in raceways, ponds or tanks in freshwater on land and then transferred to net pens or cages in the sea.

The Scottish Environment Protection Agency (SEPA) [28] is charged with regulating the fish farming industry in Scotland. In this role SEPA has to approve site-specific discharge consents for veterinary medicines, which are authorised for use in fish. SEPA has produced a procedures manual "Regulation and monitoring of marine cage fish farming in Scotland" [29] to assist applicants to comply with the regulations concerned with fish farming. SEPA are presently working on a freshwater fish farm manual to cover their regulation of freshwater fisheries.

In order to carry out an environmental risk assessment for a medicine used in fish the $PEC_{surfacewater}$ has to be calculated. SEPA have developed models to estimate exposure from the use of medicines applied by bath treatment and from the use of medicines administered in feed. These models are described in Annexes G and H of the procedures manual. This manual can be found at the SEPA website at http://www.sepa.org.uk/aquaculture/policies/index.htm.

Applicants should refer to the SEPA manual for models to calculate the $PEC_{surfacewater}$ for the initial assessment of environmental risk from veterinary medicines used in aquaculture. If further assessment of the risks from the proposed aquaculture product is required then applicants are advised to contact the regulatory authorities in the target markets for advice.

This advice may be updated if suitable models and guidance documents are made available from other sources.

4.3.3 Further Assessment

For guidance on the risk assessment of secondary poisoning the reader is referred to section 3.3.2

5. Intensively Reared Animal Branch

5.2. Tier A

5.2.2 Calculation and comparison of the PECsoil

The method of calculation the $PEC_{soil\text{-}initial}$ is described in Chapter 5 of this guidance. In accordance with the Phase II guideline it is necessary at this stage to consider the possibility of build up of active in the soil if the compound is persistent. The method for calculation of a plateau PEC_{soil} value has been described in section 2.7 'Biodegradation' in this chapter. The Phase II guideline also describes the possible methods of refining the $PEC_{soil\ initial}$ if this is required. The methods for refining the $PEC_{soil\ initial}$ can also be found in section 3.1.4.1 of this chapter.

5.2.3 Calculation and comparison of the PEC $_{water}$

In the VICH guideline it is noted that VMPs administered to intensively reared animals have the potential to impact non-target species in surface waters indirectly due to transport of the active ingredient to water either in the soil water or when adsorbed to soils. Transport to surface water can either occur via run-off or drainage. It is also possible that the active ingredient will leach to groundwater with the potential to cause adverse effects on drinking water supply. Therefore, it is necessary to calculate PEC values for both surface and groundwater.

It is recommended that when calculating the PEC values for groundwater and surface water a stepwise approach should be followed, using simple equations to provide an initial standard assessment and moving on to more complex modelling approach when a more refined estimate of exposure is required.

STEP 1

Calculation of the $PEC_{groundwater}$

The $PEC_{groundwater}$ is calculated using the approach described in the EU TGD [18]. In this model partitioning depends on equilibrium sorption to solids, no saturation at binding places and steady-state conditions. Movement, dilution, desorption, transformation, weather or crops are not considered. Soil is defined through compartment volumes for solids, water and air, dry bulk density and texture (mineral and organic fraction). Depending of the mixing depth in the soil, the groundwater level is defined.

The model calculation of the concentration in groundwater is as follows:

$$PEC_{groundwater} = PEC_{porewater}$$ Equation 32

$$CONVsoil = \frac{RHO\text{soil}}{F\text{solid}_{\text{soil}} \cdot RHO\text{solid}}$$ Equation 33

$$PECsoil_{\text{initial_pw_ww}} = \frac{PECsoil_{initial}}{4}$$ Equation 34

$$PECsoil_{\text{initial_pw_ww}} = \frac{PECsoil_{\text{initial_pw_dw}}}{CONV_{\text{soil}}}$$ Equation 35

$$PEC_{groundwater} = \frac{PECsoil_{initial_pw_ww} \times RHO_{soil}}{K_{soil-water} \times 1000}$$ Equation 36

$$K_{soil-water} = \left(Fair_{soil} \times K_{air-water}\right) + Fwater_{soil} + \left(Fsolid_{soil} \times \frac{Kp_{soil}}{1000} \times RHO_{solid} \right)$$ Equation 37

$$K_{air-water} = \frac{VP \times MW}{SOL \times R \times TEMP}$$ Equation 38

$$Kp_{soil} = Foc_{soil} \times K_{oc}$$ Equation 39

where:

$PEC_{groundwater}$	=	Predicted Environmental Concentration in groundwater [$\mu g.l^{-1}$]
RHO_{soil}	=	Bulk density of fresh soil [1700 $kg.m^{-3}$]
RHO_{solid}	=	Density of soil solids [2500 $kg.m^{-3}$]
$Fair_{soil}$	=	Fraction air in soil [0.2 $m^3.m^{-3}$]
$Fwater_{soil}$	=	Fraction water in soil [0.2 $m^3.m^{-3}$]
$Fsolid_{soil}$	=	Fraction solids in soil [0.6 $m^3.m^{-3}$]
Foc_{soil}	=	Weight fraction organic carbon in soil [0.02 $kg.kg^{-1}$]
TEMP	=	Temperature at air-water interface [285 K]
R	=	Gas constant [8.314 $Pa.m^3.mol^{-1}.K^{-1}$]
VP	=	Vapour pressure [Pa]
MW	=	Molar mass [$g.mol^{-1}$]
SOL	=	Water solubility [$mg.l^{-1}$]
$K_{soil\text{-}water}$	=	Partition coefficient solids and water in soil (v/v) [$m^3.m^{-3}$]
Kp_{soil}	=	Partition coefficient solids and water in soil (v/w) [$l.kg^{-1}$]
$K_{air\text{-}water}$	=	Partition coefficient air and water in soil [$m^3.m^{-3}$]
K_{OC}	=	Water-organic carbon distribution coefficient [l.kg]
$CONV_{soil}$	=	Conversion factor from dry weight to wet weight soil [1.13 kg_{dw} kg_{ww}^{-1}]
PEC$soil_{initial_pw_dw}$	=	Predicted initial environmental concentration in dry weight soil, corrected for a soil depth of 20 cm (i.e. $PEC_{soil\text{-}initial}/4$)
PEC$soil_{initial_pw_ww}$	=	Predicted initial environmental concentration in wet weight soil, corrected for a soil depth of 20 cm (i.e. $PEC_{soil\text{-}initial}/4$)

The scenario does not consider a typical pH range. Therefore, substance input will have to consider the pKa of the substance and pH related sorption. When the pKa is outside the range 3 to 7 no difference in behaviour between soil types is expected. When the pKa values fall within this range the pH dependence should be investigated.

Sorption is modelled through K_{OC}, and other types of sorption are not accounted for.

The $PEC_{groundwater}$ calculated using the above model should be compared with the value of 0.1 µg/l and if the $PEC_{groundwater}$ is greater than this value then the PEC_{soil} could be refined based on metabolism data. After this more sophisticated models for estimating the $PEC_{groundwater}$ should be used.

Calculation of the $PEC_{surfacewater}$

As a first estimate of the $PEC_{surfacewater}$, it can be assumed that one part run-off water will be diluted by two parts receiving water. Hence, to determine the concentration in surfacewater ($PEC_{surfacewater}$) the concentration in porewater ($PEC_{porewater}$) has to be divided by 3.

$$PEC_{surfacewater} = \frac{PEC_{porewater}}{3}$$ Equation 40

where:

$PEC_{surfacewater}$ = Predicted Environmental Concentration in surfacewater [$\mu g.l^{-1}$]

The $PEC_{surfacewater}$ value calculated using the above calculation should be compared with the PNEC values for each of the aquatic species tested. If the RQ values for any of the trophic levels exceed 1 then the PEC could be refined based on metabolism data. If the RQ is still > 1, more sophisticated models can be used to estimate the initial $PEC_{surfacewater}$. If the PEC/PNEC is still > 1, chronic toxicity data have to be provided to refine the PNEC. This PNEC has then to be compared with the chronic exposure levels. These can only be determined using the FOCUS models. For this purpose, the time weighted average PEC should be set equal to chronic exposure time of the most sensitive species tested.

Calculation of the $PEC_{sediment}$

Concentrations in sediment can be determined by the concentrations in water and the sediment-water partitioning coefficient, using the following equations:

$$PEC_{sediment} = \frac{K_{sed-water}}{RHO_{sed}} \times PEC_{surface\ water} \times 1000 \times CONV_{sed}$$ Equation 41

where:

$PEC_{sediment}$ = Predicted environmental concentration in sediment [$\mu g.kg_{dwt}^{-1}$]

$K_{sed\text{-}water}$ = Sediment-water partition coefficient [$m^3.m^{-3}$] from Equation 17

RHO_{sed} = Bulk density of sediment [1300 $kg_{wwt}.m^{-3}$]

$PEC_{surfacewater}$ = Concentration in surface water [$\mu g.l^{-1}$]

$CONV_{sed}$ = Conversion factor for sediment concentrations: wwt to dwt [$kg_{wwt}.kg_{dwt}^{-1}$] from Equation 18

Kp_{sed} = Partition coefficient solids and water in sediment [$l.kg^{-1}$] from Equation 19

1000 = Conversion factor for litre to m^3 [1000 $l.m^{-3}$]

If the $PEC_{sediment}$ has to be expressed on a wet weight basis the expression $CONV_{sed}$ is omitted from Equation 41.

STEP 2

Advanced models for PECs in groundwater and surface water

The simple equations described above provide worst-case estimates of the likely concentrations of the active ingredient in groundwater and surface waters. If RQ values for surface water organisms are ≥1 and/or the $PEC_{groundwater}$ is > 0.1 µg/l then it is advisable to use a more advanced model to predict the movement of the active ingredient to groundwater and surface waters.

The options available for more sophisticated modelling are the VetCalc model and the suite of models developed by the FOCUS (Forum for the Coordination of Pesticide Fate Models and Their Use) [30] group. Preference is given to the FOCUS models as these tools are widely accepted throughout the EU for the exposure assessment of plant protection products, which enters the environment via the same agricultural soils. In addition, the FOCUS surface water and groundwater scenarios were developed identifying highly vulnerable locations associated with agriculture.

FOCUS

A series of more complex, mechanistic environmental models and accompanying scenarios have been created by work groups in Europe known as FOCUS to simulate the fate and transport of agrochemicals in the environment. FOCUS models are designed for the exposure assessment of pesticides so they have to be tailored for the exposure assessment of a veterinary medicine.

FOCUS soil calculations are reasonably straightforward and are based on the rate of degradation of the applied chemical in a fixed soil depth, ignoring potential losses due to volatilisation, runoff, and leaching. Recent changes to the FOCUS soil guidance include a recommendation that "best fit" degradation kinetics be used rather than exclusively relying on conventional first-order fits to experimental data. The implementation of the approach used by FOCUS for veterinary products would require determination of equivalent application rates to soil (i.e. mass of chemical per land area) as well as evaluation of the appropriate degradation kinetics of the compound in soil.

GROUNDWATER

Groundwater calculations developed by FOCUS involve the simulation of the leaching behaviour of agrochemicals using a set of four models (PEARL, PELMO, PRZM and MACRO) in a series of up to nine geographic settings with various combinations of crops, soils and climate. Groundwater concentrations are estimated by determining the annual average concentrations in shallow groundwater (1m soil depth) for a period of 20 consecutive years, rank ordering the annual average values and then selecting the 80th percentile value for comparison with the 0.1 µg/l drinking water standard that has been established in the EU.

In FOCUS GW no tool for the application of the pesticide has been implemented because it was not considered critical for leaching.

When using the FOCUS models, a simple first step of this assessment can be based on a realistic worst-case FOCUS scenario. Calculations by FOCUS [30] showed that the Hamburg, Okehampton and Piacenza scenarios gave the highest leaching concentrations of all scenarios for a few model substances (both for the PEARL, PRZM and PELMO models). The Hamburg scenario is considered not representative for areas with high intensity of livestock production. The Piacenza scenario is currently being reviewed by the FOCUS Groundwater Workgroup. It is likely that this scenario will be redefined by this workgroup because its representativeness is currently considered questionable. Thus it seems most appropriate to base such a leaching assessment on the FOCUS Okehampton scenario.

The FOCUS groundwater scenarios have been parameterised both for the PELMO, PRZM and PEARL models. Boesten [31] showed that there are systematic differences in the leaching concentrations between these models: the PEARL model results usually in calculated leaching concentrations for the FOCUS groundwater scenarios that are higher than those calculated with PELMO or PRZM. EFSA [12] recommended performing leaching assessments always with PEARL and PELMO or PRZM to be sure that the leaching assessment is conservative enough.

The first step on the leaching assessment for veterinary drugs should be based on calculations for the Okehampton scenario with an application date two weeks before emergence of winter cereal (i.e. 3 October). Application in autumn is most appropriate for a conservative first step because it results usually in higher leaching concentrations than application in any other season [32] and because manure may be applied in autumn. Incorporation of the dose into the top 20 cm of soil should be used because this is typical for manure.

FOCUS [30] showed that PEARL gave higher leaching concentrations than PELMO or PRZM for five model substances considered for the Okehampton scenario. It is therefore appropriate to use PEARL for this leaching assessment.

In order to simplify the first step in the refined exposure assessment calculations were performed with FOCUS_PEARL v3.0 applying a dose of 1 kg/ha at 3 October every year over a 20-year period. The dose was incorporated into the top 20 cm of soil. The crop was winter cereal. All substance properties except K_{OM} and DT_{50} were equal to the model substance D as defined by FOCUS [30]. Runs were carried out with 90 K_{OM} - DT_{50} combinations covering FOCUS leaching concentrations ranging from 0.001 to about 100 µg/l. The results were fitted to a metamodel to be able to estimate leaching concentrations without running a FOCUS scenario.

The metamodel

Van der Zee and Boesten [33] gave the following solution for the fraction of pesticide that leaches below a certain depth assuming piston flow:

$$F = \exp\left(-\frac{k(\theta + \rho\, f_{OM}\, K_{OM})L + PSL}{q}\right) \qquad \text{Equation 42}$$

where

F	=	The mass fraction leached
L	=	The depth considered [m],
k	=	The first-order transformation rate coefficient [d^{-1}]
θ	=	The volume fraction of water [-]
ρ	=	The dry bulk density of the soil [$kg.l^{-1}$]
f_{OM}	=	The organic carbon content [$kg.kg^{-1}$]
K_{OM}	=	The organic-matter/water distribution coefficient [$l.kg^{-1}$]
P	=	The transpiration stream concentration factor [-]
S	=	The water uptake by plant roots, i.e. the sink term of Richards equation [d^{-1}]
q	=	The volume flux of water [$m.d^{-1}$].

A close correlation between F and the FOCUS leaching concentration can be expected. Based on this the following regression model can be used:

$$C_{FOCUS} = C_0 \exp\left(-\frac{k(\theta + \rho\, f_{OM}\, K_{OM})L + PSL}{q}\right) \qquad \text{Equation 43}$$

where

C_0 = The leaching concentration when 100% leaching occurs

C_{FOCUS} = The FOCUS leaching concentration (µg.l^{-1}).

After linearisation via logarithmic transformation, this leads to the following regression model (considering only K_{OM} and DT_{50} as explanatory variables because all other system properties are kept constant in the leaching calculations for the Okehampton scenario):

$$\ln C_{FOCUS} = \alpha_0 - \alpha_1 \frac{1}{DT_{50}} - \alpha_2 \frac{K_{OM}}{DT_{50}}$$ Equation 44

In which α_0 [ln(µg.l^{-1})], α_1 (d), and α_2 [l.d. kg^{-1}] are the regression coefficients. Note that α_0 has a complicated unit.

The results of the calculations with the 28 K_{OM} - DT_{50} combinations were fitted to Equation 44 using linear regression. The values of the regression coefficients were:

α_0 = 3.315 ± 0.147 ln (µg.l^{-1})

α_1 = 5.12 ± 0.62 d

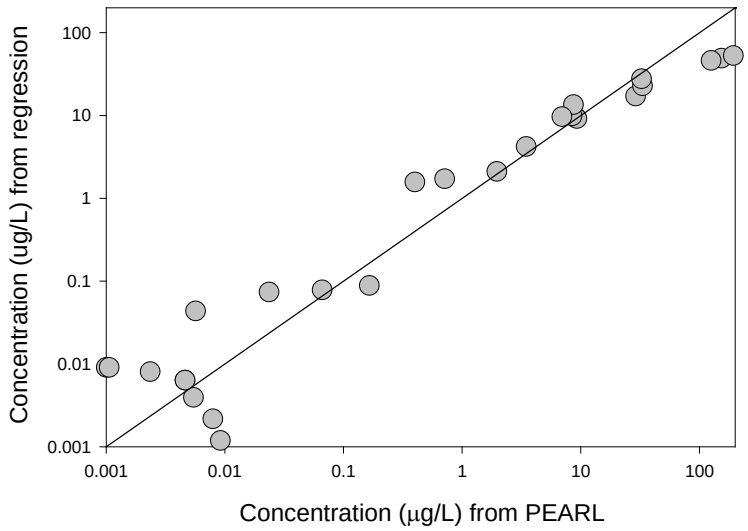
α_2 = 0.870 ± 0.021 l.d.kg^{-1}

Using these values Equation 44 can be rewritten as:

$$C_{FOCUS} = 27.53 \exp\left(-\frac{5.12}{DT_{50}} - \frac{0.870\ K_{OM}}{DT_{50}}\right)$$ Equation 45

Figure 2 shows a comparison between fitted values of C_{FOCUS} and values of C_{FOCUS} that were calculated with PEARL. The correspondence is in general acceptable although differences of up to about a factor 10 may occur. Equation 44 tends to overestimate concentrations in the range up to 1 µgl^{-1} and to underestimate concentrations above 10 µg/l. This is no problem in the risk assessment because Equation 44 provides conservative estimates in the critical range, i.e. approximately 0.1 µg/l.

Figure 2. Comparison of leaching concentrations as calculated with PEARL with leaching concentrations calculated with Equation 45. The points are concentrations and the line is the 1:1 line.



Equation 44 can be rearranged into:

$$K_{OM} = -\frac{\alpha_1}{\alpha_2} + \left(\frac{\alpha_0 - \ln C_{FOCUS}}{\alpha_2} \right) DT_{50} \qquad \text{Equation 46}$$

So Equation 46 shows that K_{OM} is a linear function of the DT_{50} for a fixed FOCUS leaching concentration, e.g. if we require that C_{FOCUS} is less than a certain value, then Equation 46 results in the requirement that the K_{OM} is larger than the expressions given in Table 10. These inequalities can be used for the first-tier leaching assessments of VMPs.

Table 10. Requirements for the K_{OM} following from Equation 46 as a function of the FOCUS leaching concentration

C_{FOCUS} (µg.l^{-1})	Requirement for the K_{OM}
0.01	K_{OM} > -5.9 + 9.1 DT_{50}
0.1	K_{OM} > -5.9 + 6.5 DT_{50}
1	K_{OM} > -5.9 + 3.8 DT_{50}
10	K_{OM} > -5.9 + 1.2 DT_{50}

Note that these relationships are based on a dose of 1 kg.ha^{-1}. In the event that the actual dose is substantially lower or higher then a less or more stringent relationship should be used in proportion to the dose (e.g. when the dose is < 0.1 kg.ha^{-1}, the relationship K_{OM} > -5.9 + 3.8 DT_{50} can be used to ensure the leaching concentrations is < 0.1 µg.l^{-1}).

If, it is not possible to exclude the likelihood that groundwater concentration is > 0.1 µg l^{-1} based on the Metamodel, then it is necessary to run the PEARL model using the scenarios applicable for the areas in which the VMP will be authorised.

When a VMP is to be authorised under the centralised procedure, representative scenarios for the different target animals could be selected based on pedoclimatic relevance and significant livestock production, as recommended for feed additives by EFSA [34].

SETTINGS OF THE FOCUS MODEL FOR GROUNDWATER

As explained above, application to arable land is most typically carried out in the early autumn. In order to standardise, the exposure assessments timing of application to soil is assumed to coincide with drilling of winter cereals (in the absence of pure grassland scenario) as these crops are typically grown throughout Europe and represent a significant input of manures on a total mass basis across Europe. It is assumed that manure will be applied at a rate of 170 kg $N.ha^{-1}$ in one spreading event. As the input in FOCUS is expressed in $kg.ha^{-1}$, the PEC_{soil} has to be converted to $kg.ha^{-1}$ before running the FOCUS model. Recommended input parameters on the application of FOCUS model is presented in Appendix I.

SURFACE WATER

The surface water and sediment calculations developed by FOCUS include three progressively refined tiers of evaluation, ranging from initial spreadsheet-based evaluations of potential aquatic concentrations to more detailed mechanistic calculations of drift, runoff, erosion and field drainage loaded into a series of small water bodies. The surface water and sediment calculations are performed using an overall calculation shell called SWASH which controls models which simulate runoff and erosion (PRZM), leaching to field drains (MACRO), spray drift (internal in SWASH) and finally aquatic fate in ditches, ponds and streams (TOXSWA). These simulations provide detailed assessments of potential aquatic concentrations in a range of water body types in up to ten separate geographic and climatic settings.

In FOCUS there are no recommendations for dates or crops for manure applications as the timing of applications of pesticides are generally much more carefully defined. However, you can set up FOCUS to apply chemical in manures to coincide with drilling for any crop implemented in any of the scenarios. This is done and covers a wide variety of irrigated and non-irrigated crops. It does not, however, include wet grassland situations that lie beyond the conditions where arable agriculture is practiced.

In FOCUS SW the PAT tool is designed to ensure applications provide a 'reasonable challenge' in terms of proximity to rainfall. It also eliminates possibility of applications occurring on rainfall days.

Detailed explanations of the FOCUS models as well as the modelling scenarios, key assumptions, required modelling inputs and model outputs are provided in the respective FOCUS modelling reports [35, 42]. The FOCUS surface water and groundwater models have been placed on a website (viso.ei.jrc.it/focus/index.htm) where they can be freely downloaded.

In an investigation performed within the ERApharm project by Schneider and Fenner [36], appropriate FOCUS and Vetcalc scenarios were selected based on (i) the potential loads of VMP excreted by livestock and (ii) environmental conditions influencing substance availability and transport to surface water. The selected FOCUS scenarios are given in Appendix II and could be used to determine for each target animal which scenario is most appropriate for the areas at which the VMP will be authorised. Some areas are only covered by VetCalc scenarios. For these areas the Vetcalc model might be more appropriate (see Appendix III).

When a VMP is to be authorised within a centralised procedure, representative scenarios for the different target animals could be selected based on pedoclimatic relevance and significant livestock production, as recommended for feed additives by EFSA [34].

SETTINGS OF THE FOCUS MODEL FOR SURFACE WATER

As proposed for groundwater, the application of manure to arable and grass land is considered to coincide with the drilling of cereals in autumn (in the absence of a pure grassland scenario). In order to

select the most appropriate date, the FOCUS PAT tool should be used. As a realistic worst case, it is assumed that manure will be applied at a rate of 170 kg.Nha^{-1} in one spreading event. Without information on the degradation in a water/sediment, the degradation rate is set to zero. As mentioned for groundwater as the input in FOCUS is expressed in kg.ha^{-1}, the PEC_{soil} has to be converted to kg.ha^{-1} before running the FOCUS model. Recommended input parameters on the application of FOCUS_model is presented in Appendix I.

RUNNING FOCUS

As the FOCUS models are designed for the exposure assessment of pesticides they have to be tailored for the exposure assessment of a veterinary medicine. Most important is that transport to surface water via spraying should be excluded. For all FOCUS models there are a large number of possible exposure scenarios built in and within each scenario there are a number of variables which need to be defined. For any particular FOCUS model all the scenarios should be run in the first instance. The loading to soil, which is necessary for running the model, will be available from the PEC_{soil} calculations carried out in the Phase I assessment. The K_{OC} and DT_{50} values should be the average values from the experimental data. The application time is most critical for run-off or drainage to surface water. For pragmatic reasons (in order to 'standardise' assessments) timing of application is assumed to coincide with drilling of winter cereals. Cereals are typically grown throughout Europe and represent a significant input of manures on a total mass basis across Europe. The FOCUS PAT tool could also be used to select the most appropriate date.

INTERPRETATION OF RESULTS FROM FOCUS

In FOCUS groundwater models the 80th percentile value for a 20-year period is presented.

The results for surface water are presented as the maximum predicted $PEC_{surfacewater}$ and the time of occurrence of the peak. The decline in concentrations after the peak is presented graphically.

In principal, $PEC_{groundwater}$ and $PEC_{surfacewater}$ values for all scenarios should be compared with the limit concentration of 0.1 µg/l for groundwater and the PNEC values for the aquatic organisms, respectively. For scenarios where the trigger value for groundwater is exceeded or the RQ values are ≥1, further consideration of the results in relation to the proposed use of the product will be needed. For example it may be that the particular 'failed scenarios' represent an area, which is a minor area of production for the particular species for which the product is indicated. Alternatively it may be possible to investigate the exposure scenario further using different manure management scenarios.

It is up to the applicant to present further assessment which may involve more modelling, more studies or relevant arguments as to why exceeding the trigger value for groundwater or the RQ for aquatic organisms is not indicative of an unacceptable risk.

For further guidance to investigate leaching to groundwater under field conditions, the reader is referred to the OECD Guidance Document [37].

Issues of uncertainty

When trying to decide whether the FOCUS fate and transport models can be used for the prediction of leaching, drainage and runoff of veterinary medicines, three major points have to be taken into account:

1. In the models, the default assumption regarding sorption is that sorption behaviour is dominated by sorption to organic carbon. Therefore, at least one of the models (MACRO) provides an option to enter a Koc value (organic carbon-water partition coefficient) to characterize the sorption

behaviour of a substance. Since veterinary pharmaceuticals could be large molecules with several functional groups and a tendency to speciate into ionic species around environmental pH values, other soil components with polar and/or charged surfaces might also act as sorbents. Additionally, sorption behaviour is known to be strongly pH-dependent. If this type of behaviour is confirmed by further studies on the sorption behaviour of pharmaceuticals, models need to be adapted to allow accounting for additional sorbents and pH-dependence of sorption.

2. Field and laboratory studies have confirmed that pharmaceuticals reach the soil in either, manure, slurry or dung, which influences their transport. Plot studies for manure application of sulfonamides have shown that the loads in runoff are 10-40 times higher when the substances are applied in manure than when they are applied in pure aqueous solution [41]. Possible explanations include physical sealing of the soil surface with fine organic matter, pH effects of the most basic manure that change the speciation status of the substances, and effects of dissolved organic matter (DOM), such as competition for sorption sites or sorption of the pharmaceuticals to mobile DOM. Other studies have shown, however, that the temporal response of runoff and leaching processes to rainfall events as well as the peak concentrations observed are very comparable to what we know from pesticides [38-40]. Studies with further compounds are therefore needed to corroborate the magnitude of the effects discussed above in order to decide at what stage of the risk assessment process they should be taken into account, if at all. In that case, the models would have to be adapted in order to be flexible enough to account for changes in the physical properties of the top soil layer as well as in the chemical properties of the substance in the top soil layer.

3. New exposure scenarios for pasture areas and (wet) grassland sites have to be defined for feed additives as well as for veterinary medicines. Within the project ERAPharm, the use of FOCUS SW scenarios for the environmental risk assessment of veterinary medicines has been evaluated [36]. A geo-referenced matrix of variables on (i) the potential loads of veterinary medicines excreted by livestock and (ii) environmental conditions influencing substance availability and transport to surface waters was used to identify areas with high a contamination potential. These areas were compared to existing scenarios from FOCUS with regard to their criticality and representativeness.

   It was found that FOCUS completely covered all relevant situations in Europe and that three situations were especially underrepresented with regard to veterinary medicines (and feed additives). These are (i) hilly areas with a cool, wet climate stretching from the Massif Central to the Bavarian Forest, (ii) foothills of mid-altitude mountain ranges stretching from Belgium to Slovakia and (iii) plains in central Spain, Hungary and Romania with a rather continental climate and heavy soils. This calls for the compilation of new sets of input parameters for the parameterization of the FOCUS models, as these scenarios are also considered relevant for areas with high stocking density. Specifically, at least one runoff scenario in hilly areas in Central Europe on slowly permeable soils as well as a drainage scenario in Eastern European plains should be defined.

Within the ERAPharm project work [43], it is planned to address the first two issues. First, sorption studies on several human and veterinary pharmaceuticals to soil, sediment and sludge will be carried out. In all cases, the sorption matrices will be characterized thoroughly with regard to pH and composition in terms of sorbents. These results should help to understand the various factors that drive sorption of pharmaceuticals. Second, column and field studies with antiparasiticides in dung will be carried out, measuring leaching, drainage and runoff. The resulting concentrations will be compared to outputs of the corresponding FOCUS models. This will give a first impression of their validity for pharmaceuticals encountered in the dung of pasture animals. A first evaluation of MACRO with experimental data (Larsbo, in preparation) showed that the model could fairly well simulate runoff and

transport of bromide and sulfadimidine and that effects of the manure matrix could be qualitatively simulated by changing hydraulic parameters in a thin surface layer. However, the information gained in the micro-plot simulations was generally not useful for the field scale and therefore, sulfadimidine losses could only be simulated satisfactorily after a very strong parameterisation of preferential flow. Additionally, similar studies will be carried out for human pharmaceuticals in sludge. These will also contribute to the understanding of the influence of various application matrices and the applicability of the FOCUS models to those situations.

6. Pasture Animal Branch

6.2 Tier A

6.2.2 Calculation and comparison of PEC_{soil}

The method of calculation the $PEC_{soil\text{-}initial}$ is described in Chapter 5 (Question 17) of this guidance. The Phase II guideline also describes the possible methods of refining the $PEC_{soil\text{-}initial}$ if this is required. The methods for refining the $PEC_{soil\text{-}initial}$ can also be found in section 3.1.4.1 'PEC refinement' in this chapter.

6.2.3 Calculation and comparison of the PEC_{dung}

The method of calculating the $PEC_{dung\text{-}initial}$ and the $PEC_{dung\text{-}refined}$ can be found in section 3.1.4.1 'PEC refinement' in this chapter.

6.2.4 Calculation and comparison of PEC water

6.2.4.1 Surfacewater and groundwater

In the VICH guideline it is noted that VMPs administered to pasture animals have the potential to impact non-target species in surface waters indirectly due to transport of the active ingredient to water either in the soil water or when adsorbed to soils. Transport to surface water can either occur via run-off or drainage. It is also possible that the active ingredient will leach to groundwater with the potential to cause adverse effects on drinking water supply. Therefore, it is necessary to calculate PECs for both surface and groundwater.

The methods described in Chapter 6, Section 5.2.3 'Calculation and comparison of the PEC water' should be used to calculate the $PEC_{groundwater}$ and $PEC_{surfacewater}$ following treatment of pasture animals. If the use of more sophisticated models is required it should be noted that the VetCalc model has specifically considered exposure of pasture by sheep and cattle.

6.2.4.2 Aquatic exposure scenarios

6.2.4.2.1 Direct excretion of active substances into surface waters by pasture animals

Exposure model for direct excretion of ectoparasiticides into surface water by cattle

On pasture drinking water for grazing cattle is often provided by natural surface waters such as a stream or pond. Cattle will enter the water to drink and will often urinate and defecate into the water at the same time. For ectoparasiticides indicated for use in cattle on pasture it is necessary to make a risk assessment of this exposure scenario. It is assumed that a pasture of 1 hectare contains a slow flowing stream defined by the parameters given in Table 11.

Table 11. Stream parameters for calculation of a $PEC_{surfacewater}$ resulting from direct defecation

Parameter	Value	Justification
Length	100 m	the pasture measures 100 x 100 m
Width	1 m	From data considered by FOCUS [42]
Depth of water (D_w)	0.3 m	
Depth of sediment (D_s)	0.05 m	
Density of wet sediment (RHO_{sed})	1300 $kg.m^{-3}$	EU TGD Part II, Chapter 2 [18]
Fraction of organic carbon in sediment (f_{oc})	0.05	

For products administered parenterally or orally the $PEC_{surfacewater}$ should be calculated using the following equation:

$$PEC_{surfacewater} = \left(\frac{D \times Ad \times BW \times SD \times Fe}{L \times W \times D_w \times 1000} \right) \times 1000 \qquad \text{Equation 47}$$

For products administered topically the $PEC_{surfacewater}$ should be calculated using the following equation:

$$PEC_{surfacewater} = \left(\frac{D \times Ad \times BW \times SD \times Fe \times Fs}{L \times W \times D_w \times 1000} \right) \times 1000 \qquad \text{Equation 48}$$

where:

$PEC_{surfacewater}$ = Predicted Environmental Concentration in the stream [$\mu g .l^{-1}$]

D = Daily dose of the active ingredient [$mg.kg_{bw}^{-1}.d^{-1}$]

Ad = Number of day of treatment [d]

BW = Animal body weight [$kg_{bw}.animal^{-1}$] (see Table 4)

SD = Stocking density [$animal.ha^{-1}$] (see Table 4)

Fe = Fraction of the total absorbed dose excreted into the stream[9] [0.01]

Fs = Fraction of the administered dose absorbed by the animal [determined from experimental data assume 1 if no data]

L = Length of stream per hectare [$m.ha^{-1}$]

W = Width of stream [m]

D_w = Depth of water in the stream [m]

1000 = Conversion factor [1000 $\mu g.mg^{-1}$] or [1000 $l.m^{-3}$]

If, based on the initial $PEC_{surfacewater}$, the RQ for aquatic invertebrates is >1 the $PEC_{surfacewater}$ can be refined based on the partitioning of the compound between water and sediment. The refined $PEC_{surfacewater}$ and the $PEC_{sediment}$ can be calculated using the following equations.

[9] It is assumed that 1% of the total dose administered to the animals in the pasture is excreted into the stream because: the cattle roam freely in the pasture and spend the same proportion of time in the stream as in any other area; excretion is as likely to occur in the stream as on the pasture.

$$PEC_{sediment} = \left(\frac{Mts}{\left(Ms + \left(\frac{\left(RHO_{sed} \times V_w \right)}{K_{sed-water}} \right) \right)} \right) \times 1000$$ Equation 49

$$PEC_{surfacewater\ refined} = \frac{Mts}{\left(\left(K_{sed-water} \times \left(\frac{Ms}{RHO_{sed}} \right) \right) + V_w \right)}$$ Equation 50

$$Ms = L \times W \times D_s \times RHO_{sed}$$ Equation 51

$$Vw = L \times W \times D_w$$ Equation 52

where:

$PEC_{sediment}$	=	Predicted Environmental Concentration in the sediment [$\mu g.kg^{-1}$]
$PEC_{surfacewater\ refined}$	=	Refined Predicted Environmental Concentration in the stream [$mg.m^{-3} \equiv \mu g.l^{-1}$]
$K_{sed-water}$	=	Sediment-water partition coefficient [$m^3.m^{-3}$] from Equation 17
Ms	=	mass of sediment [kg]
Mts	=	total mass of compound in the water system [mg]
V_w	=	Volume of water in the system [m^3]
L	=	Length of stream [m]
W	=	Width of stream [m]
Ds	=	Depth of sediment [m]
Dw	=	Depth of the water system [m]
RHO_{sed}	=	Bulk density of wet sediment [1300 $kg.m^{-3}$]
1000	=	Conversion factor [1000 $\mu g.mg^{-1}$]

If this refinement is necessary then the risk to sediment dwelling organisms needs to be assessed as described in section 3.2. If the toxicity data is expressed on a sediment dry weight base the $PEC_{sediment}$ has to be converted accordingly, using Equation 18.

6.2.4.2.2 Contamination of hard standing areas during application of topical ectoparasiticides, leading to indirect exposure of the aquatic environment through the run-off from these surfaces following rainfall

There is currently no appropriate exposure model for this scenario. However, research in this area is ongoing. A model for this scenario might be included at a later date depending on the results of the research.

6.2.4.2.3 Entry of animals treated with high volume ectoparasiticides into surface waters leading to direct exposure of the aquatic environment

Exposure model for direct entry into surface water from run off from treated sheep

Following treatment of sheep carrying an appropriate amount of wool using the correct dosing procedure there will be run off of some of the applied dose. It is possible that these treated animals will cross a small stream shortly after treatment on the way back to pasture. This will result in the contamination of the watercourse with the active ingredient.

A model for this scenario can be proposed based on the following assumptions:

- The volume lost per animal in the first hour after treatment with a pour-on product is 5% of that applied. (This value can be replaced by an actual value if appropriate study results are available.)
- 100 sheep cross watercourse 30 cm wide by 30 cm deep over a length of 10 m of water. The animals take 1 minute to cross the stream and as a result 1/60th of the volume lost per animal in the first hour after treatment enters the water
- This feeder stream enters a larger stream or a small river, where it is diluted by a factor of 3

The $PEC_{surfacewater}$ can be calculated using the following equation.

$$PEC_{stream} = \frac{Va \times Fl \times C \times Tcr \times 1000 \times N_sheep}{L \times W \times D_w \times 1000}$$ Equation 53

where:

PEC_{stream} = Predicted environmental concentration in the stream [µg.l^{-1}]

Vα = Volume applied to each animal [ml]

Fl = Fraction lost in 1 hour [0.05 unless data are available]

C = Concentration of active in the product [mg.ml^{-1}]

Tcr = Fraction of minute taken to cross the stream [0.017]

L = Length of stream [m]

W = Width of stream [m]

D_w = Depth of water in the stream [m]

1000 = Conversion factor [1000 µg.mg^{-1}] and [1000 l.m^{-3}]

N_sheep = Number of sheep [100]

The $PEC_{surfacewater}$ in the larger stream/river receiving water from the stream can be calculated as follows:

$$PEC_{river} = \frac{PEC_{stream}}{Dil_s}$$ Equation 54

where:

PEC_{river} = Predicted environmental concentration in surfacewater in the river [µg.l^{-1}]

PEC_{stream} = Predicted environmental concentration in surfacewater in the stream [µg.l^{-1}]

Dil_s = Dilution in receiving stream [3]

If the RQ values for aquatic organisms in the stream are <1 then further refinement, i.e. by calculation of the PEC_{river} is not needed. If the RQ values are ≥1 then the PNECs should be compared to the PEC_{river}. If these RQ values are ≥1 then further refinement based on sediment partitioning as described in section 6.2.4.2.1 should be carried out. The assessment would then proceed as in section 6.2.4.2.1.

7. Screening for PBT/vPvB substances

Persistent, bioaccumulative and toxic substances (PBT) as well as very persistent and very bioaccumulative chemicals (vPvB) are of particular concern since their rate of disappearance is lower than their rate of release into the environment resulting in build-up in the environment over time. The concern is that such a build up could result in effects that are difficult to reverse and to detect at an early stage. A risk of chronic exposure and for long term and cumulative adverse effects lead to a very high uncertainty in making a determination of the predicted environmental concentration (PEC) via established exposure models and/or establishing the predicted no effect level (PNEC) from standard laboratory tests. As a result there is a higher uncertainty in risk evaluation. In the EU substance and products assessment strategy special regard is given to PBT/vPvB substances.

The intrinsic properties of individual substances, specifically whether they are persistent (P), toxic (T) or liable to bioaccumulate (B), determine whether they fall within the definition of a PBT/vPvB substance. The cut-off values for each of these criteria are given in the EU TGD for industrial chemicals and biocides [18].

8. REPORTING

This Chapter provides some instructions on communicating the reliability of tests and a template for the layout of an environmental impact assessment report. The Chapter is meant for regulators in competent authorities, but may be used by applicants.

8.1 GENERAL INFORMATION ON THE STRUCTURE OF SUMMARIES

8.1.1 Instructions

OECD Guidelines and other International Guidelines are the starting points for the instructions. The instructions are of a technical nature: it is stated which information has to be dealt with, and in which way, and how to apply this information in the models and decision schemes without an extensive explanation of all the rationales.

In this way the instructions function as a checklist for preparing the Summaries and the Assessment Report (AR). It should also be noted that this document is not a cookery-book (which would result in uniform assessment reports): expert judgement remains *crucially* important in the process of evaluating the environmental aspects of substances.

8.1.2 Reliability of information

All delivered test reports are summarised and evaluated on their scientific validity and their usefulness by the reviewer according to this document, whether or not they are required for the Phase I or II assessment.

All the studies that are summarised and evaluated in an AR, are given a Reliability Index (RI) as a measure for the *reliability* (i.e. the intrinsic reliability of a test with respect to the methodology and the description).

Table 12. The structure of an index, which describes the reliability of studies.

Reliability index (RI)	**Definition**	**Description**
1	Reliable	The methodology and the description are in accordance with the instructions in this guideline
2	Less reliable	The methodology and/or the description are less in accordance with the instructions in this guideline
3	Not reliable	The methodology and/or the description are not in accordance with the instructions in this guideline

The RI is found in the Header of every summarised test in an assessment report. It is an obligatory record for the reviewer. Although usefulness indicators are not yet developed, there are already instructions on the usefulness of data. From these definitions it follows that reliability plus usefulness equals quality.

8.1.3 Instruction tables

The instruction tables (or summary tables) are the core of the instructions. The summary tables structure the abundance of information and help assigning a RI to the tests. Table 13 is an example. It starts with the 'description' including the relevant test conditions, followed by the 'results' with the relevant test results and it ends by 'pay attention' including those items that should be checked, but need not necessarily be included in the Summary.

In the summary tables one finds the requirements, which have to be met for a study; the items refer to the reliability of a test. Items that refer to the usefulness rather than to the reliability are given in the footnotes of the Table. One may dispute whether certain test items fall within reliability or usefulness. One may argue whether the item on the λ of the light source in a photolysis test in water, implies that a test with λ <290 nm is less reliable or that such a test is less useful as the λ does not reflect natural conditions. In this way the summary tables keep on fostering discussions. The tables should therefore not be seen as too compelling.

If items reported are not in accordance with the summary tables, the reliability of a study decreases. In the column with the heading 'Reliability lower?' this is indicated by a **Y**(es) or an **E**(xpert judgement):

Y. Y(es) indicates that solely based on not fulfilling this requirement for this item, the reliability of the entire study is expected to decrease. This can be reflected in assigning an RI of 2 to a test, or even an RI of 3. It is up to expert judgement in the latter case, to decide how many "Y"-items are required for assigning an RI of 3 to a particular test.

E. E(xpert judgement), indicates that no clear guidance can be given. The reviewer can consult a specialist.

It should always be stated clearly in a Summary under Remarks why a certain RI has been assigned, so that this can be verified.

Table 13. - Example of a summary table

	Items	**Notes**	**Reliability lower?**
Description	**These items should always be included in the test description in a Summary.**	These notes explain the requirements, which have to be met for a reliable test (i.e. with an adequate methodology and description). If items in a study deviate from these requirements, check in the next column ("reliability lower?") whether the reliability with respect to that particular item may decrease. **Y**(es) This note indicates that the reliability can be considered to decrease. **E**(xpert judgement) This note indicates that the	 Y E

	Items	Notes	Reliability lower?
		assignment of an RI is up to the reviewer.	
	These items should only be included, if a test is not performed according to a Guideline.		
Results	**These results should always be included, under Results.**		
Pay Attention	The items here should not necessarily be included into a Summary, but should be checked. These items —if deviating from the requirements— can be included under Remarks.		

Assessment Report Template

PHASE I

1. DESCRIPTION OF THE PRODUCT

2. INTRODUCTION

3. PATTERN OF USE AND RELEVANT EXPOSURE ROUTES

4. PHASE I ASSESSMENT

4.1 Model calculations

4.2 Concentrations in the environment

5. CONCLUSIONS PHASE I

PHASE II

Tier A

6. SUMMARY OF AVAILABLE DATA

6.1 Physico-chemical properties

6.2 Fate and behaviour

6.2.1 Metabolism and excretion

6.2.2 Degradation

6.2.3 Soil adsorption

6.3 Toxicity

6.3.1 Soil organisms

6.3.2 Water organisms

6.3.3 Dung fauna

7. PEC CALCULATIONS (EXPOSURE ASSESSMENT)

7.1 Soil

7.2 Groundwater

7.3 Surface water

7.4 Sediment

7.5 Dung

8. PNEC CALCULATIONS (EFFECT ASSESSMENT)

8.1 Soil

8.1.1. PNEC Dung

8.1.2 PNEC micro-organisms

8.1.3 PNEC earthworms

8.1.4 PNEC plants

8.1.5 Relevant PNECs for other non-target animals

8.2 Groundwater

8.3 Surface water

8.3.1 PNEC algae

8.3.2 PNEC daphnia

8.3.3 PNEC fish

8.3.4 PNEC for other non-target animals

8.4 Sediment

8.4.1 PNEC sediment organisms

9. RISK CHARACTERISATION

9.1 Soil

9.2 Groundwater

9.3 Surface water

9.4 Sediment

10. PEC REFINEMENTS

11. REFINED RISK CHARACTERISATION

12. CONCLUSIONS TIER A

Tier B

13. PNEC REFINEMENTS

13.1 Soil

13.1.1 PNEC micro-organisms

13.1.2 PNEC plants

13.1.3 PNEC Dung

13.2 Surface water

13.2.1 PNEC algae

13.2.2. PNEC daphnia

13.2.3 PNEC fish

13.3 Sediment

14. BIOCONCENTRATION IN BIOTA

15. RISK CHARACTERISATION

16. CONCLUSIONS TIER B

Tier C

17. FIELD STUDIES

18. CONCLUSIONS TIER C

19. QUESTIONS TO THE SPONSOR

20. EXPERT REPORT / STATEMENT

21. STUDY SUMMARIES (EXTENDED)

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APPENDIX I - Application of FOCUS models

GROUNDWATER

Input parameters PEARL

1. Scenario:
Location: → Okehampton
Crop Calendar: → *WCEREALS*
Irrigation: → irrigation scenarios are considered for Chateaudun, Piazenca, Sevilla, Thiva; *No irrigation* in the other cases.
Tillage: → *No tillage*
Repeat interval for application events (a): → 1

2. Simulation Control:
Start date: → 01/01/1901
Stop date: → 31/12/1926
Stop criterion (kg/ha): → default zero
Repeat hydrology: → no tick
Although the total time is 26 years, the protocol on the reactive tracer will be for only 20 years.

3. Output Control:
Summary report: → pick FOCUS report
No additional changes.

4. Swap Hydrological Method:
Option Hydrology: → *Run SWAP and then PEARL only*
No additional changes.

5. Substance:
General
Molar mass (g/mol): → enter value
Saturated vapour pressure (Pa): → enter value
Molar enthalpy of vapourisation (kJ/mol): → 95 (default pesticides)
Solubility in water (mg/l): → enter value
Molar enthalpy of dissolution (kJ/mol): → 27 (default pesticides)

Freundlich sorption
K_{OM}: → enter value (K_{OM} = K_{OC} / 1.724)
No additional changes.

Transformation
Half-life (d): → enter value

No additional changes.

Diffusion

No changes, use default settings from pesticides.

Crop

Wash-off factor (m^{-1}): → ≥ 10^{-6}, even if there is no wash-off.

Coefficient for uptake by plant: → no uptake

6. Application

Advice should be given, which application form is most appropriate for VMPs. Since for VMPs either arable land or grassland without harvest is considered, *absolute application* seems more appropriate than *relative application*.

As the input in FOCUS is expressed in $kg.ha^{-1}$, the PEC soil has to be converted using the following equation:

$Application\,rate[kg.ha^{-1}] = \frac{PEC_{soil}[\mu g.kg^{-1}] \times depth_{soil}[m] \times bulk\,density[kg.m^{-3}]}{100000}$	Equation 55

Absolute applications

Application type: → either *incorporation* or *application to the soil surface*

Date: → enter date of application (pre-emergence)

Dosage (kg/ha): → enter value

Depth (m): → soil depth used to calculate PEC_{soil}

7. Deposition

No deposition

SURFACE WATER

SWASH

1. Actions/ Create view and edit substances

General:

- Enter information on chemical properties (molar mass, vapour pressure, solubility in water, metabolism).
- For molar enthalpy of vaporisation and dissolution and diffusion coefficients in water and air the default values from pesticides may be used.
- Maybe a short comment regarding the applicability of the default values especially to macromolecules should be inserted, since these properties are generally assumed to be substance specific.

Sorption

- Enter either K_{OM} or K_{OC}, the other value will be calculated internally.

- Enter Freundlich exponent. (The corresponding Freundlich exponent for soil or sediment is internally calculated from the given K_{OM} or K_{OC} value and the fraction of organic matter in the soil of the chosen scenario.)
- Ref. concentration in the liquid phase [g/m³]: This refers to the concentration at which the sorption parameters were determined. If it was at 1 g/m³, then the default value of 1 is correct. In case the concentration was significantly different from 1 g/m³, the appropriate value should be inserted. This is then used for internal correction of the Freundlich parameters.

Uptake and wash-off

- Do not assume any plant/ root uptake or wash off. Hence, set all parameters zero.

Transformation:

- Enter DT_{50} in water, soil and sediment and the respective temperatures.
- If you assume no transformation in the crop (or no data are available), set a large DT_{50} in crop (e.g.10^3).
- Effect of temperature: Use default value from pesticides if now data are available.
- Specifications on transformation in soil: Use default values from pesticides for the dependence of transformation on soil moisture/ water content.

2. Focus wizard

- Use W*cereals* for crops selection. Although more realistic, a pure grassland scenario is not available. Root uptake zero has to be set to zero (in the window "*uptake and wash off*").

3. User defined wizard

- Selected crop according to the chosen crop above.
- Accept selected water body types.
- Accept appropriate scenarios.

4. View projects and define applications

- View and edit application: Enter number of applications, as well as the application mode (granular application is the closest scenario to manure spreading). For run-off scenarios the depth of incorporation is also required.

APPENDIX II - Geographic coverage and characteristics of selected run-off and drainage scenarios for VMPs and their overlap with existing FOCUS and VetCalc scenarios taken from the ERAPharm project.

	Coverage	Characteristics	Existing scenarios
1	Po valley, Central France, Northern Netherlands	Lowlands with permeable soils over shallow groundwater. Intensive livestock production.	FOCUS D5 and potentially R3, VetCalc Emilia Romagna
2	Bretagne and Normandy, Ireland, Belgium and Southern Germany	Mild and humid climate. Hilly areas with loamy soils, mixed arable and grassland use. Intensive animal production of cows, cattle and pigs.	VetCalc Bretagne, potentially FOCUS D5 and D2
3	Western England & Wales, Western Ireland, Galicia, West coast of Norway	Cool and wet climate, exlusively grassland on impermeable soils with high OC content, relatively close to waters, intensive animal production of dairy cows, cattle and sheep on grassland.	VetCalc Wales
4	Southern France, southern foothills of Pyrenees, Alps and Apennine, Styria and Epirus	Areas with wet and mild climate and high precipitation intensity. Permeable soils on moderate slopes. Intensive livestock production.	VetCalc Midi-Pyrenees, FOCUS R4
5	Netherlands, Northern Germany, Denmark, Central France and Eastern England	Flat areas with humid climate and sandy soils. Intensive arable cropping and animal production, mainly pigs and dairy cows.	FOCUS D4, VetCalc Noord Brabant, VetCalc Denmark
6	Massiv Central, Vosges, Bavarian Alps and Forest, Northern and Southern Norway	Hilly areas with cool climate, high frequency of extreme rainfall, sandy soils with high OC content. Dairy production on grassland.	
7	Wallonia, Rhineland, central German mountain ranges, foot-hills of mountain ranges in the Czech Republic	Hilly areas with moderate climate but relatively high precipitation intensity. High OC content in soils. Moderate livestock production, mainly cows and cattle.	
8	Central Spain, Italy, Greece, Bulgarian and Romanian lowlands	Riverbeds and coastal areas with Mediterranean climate and permeable soils influenced by groundwater. Swine, poultry and sheep production.	FOCUS D6 and potentially R4
9	Northern France, Belgium, Southern England and Poland	Plains dominated by arable soils with high content of sand and silt. Pig and poultry production.	FOCUS R1 and D4
10	Northern France, Central Germany, Czech Republic and Slovakia, Hungary, Southern Sweden	Similar to 9. Plains with primarily arable use of light, silty soils. Moderate climate. Important pig production.	FOCUS R1 and D4
11	Lorraine, Central Germany, Hungary	Related to 9 and 10, but soils with higher clay content. Intensive pig production.	FOCUS R1 and D5, VetCalc Brandenburg
12	Central and Eastern Spain, lowlands in Hungary, Romania and Bulgaria	Lowlands with clay-loamy soils with a dry and mild climate. Important pig and poultry production	
13	Central and Eastern Spain, Romanian lowlands	Related to 12, but hilly areas with steeper slopes, less clay in soil and a dry climate. Intensive sheep production.	FOCUS D6
14	Northern Portugal, South-Western foothills of Alps, Pyrenees and Apennine, Slovenia	Mild and wet climate, high occurrence of extreme rainfall on steep slopes mainly covered by grassland. Moderate livestock production	FOCUS R2
15	Northern Germany, Eastern Denmark, Poland and Czech Republik	Plains with sandy soils and mainly arable use. Important production of pig, poultry and dairy cows.	VetCalc Brandenburg FOCUS D4
16	Western Denmark, Brandenburg, Eastern Lithuania	Similar to 15, but with sandier soils and slightly less arable use and shorter distance to rivers.	VetCalc Brandenburg FOCUS D4
17	Eastern England, Northern Germany, Poland and Baltic states	Related to 16, but heavier soils over shallow groundwater. Intensive poultry and pig production	VetCalc Brandenburg FOCUS D2
18	Northern Germany, Poland	Similar to 16, with higher permeability of soils	VetCalc Brandenburg

APPENDIX III - Model description of VetCalc

This model was developed by Cambridge Environmental Assessments (CEA) using funding from Defra in the UK. VetCalc estimates PEC values for groundwater and surface water for 12 predefined scenarios which were chosen on the basis of the size and importance of their livestock production and its diversity, the range of agricultural practice covered by the scenarios and the desire to cover three different European climate zones (Mediterranean, Central and Continental Scandinavian). Each of the scenarios has been ranked in terms of its importance as a scenario for each livestock species. The model also includes for each scenario the typical manure management practices for the region on which the scenario is based. Summary details of the 12 scenarios are presented in the following Table.

Summary of VetCalc scenarios

Region	Soil type	Climate type	Potential to cover other regions	Similarity to FOCUS scenarios
Spain - Andalucia	sandy silt loam	Mediterranean	Portugal	None
Italy - Emilia Romagna	clay loam	Mediterranean	None	FOCUS SW R3
Netherlands - Noord Brabant	sand	Central	Belgium (Vlaanderen); Germany (Nord Rhein Westfalia)	FOCUS SW D3
Denmark	loamy sand	Central	Germany (Schleswig Holstein)	FOCUS SW D3
France - Bretagne	sandy loam	Central	None	None
UK - Yorkshire	sandy loam	Central	None	None
France - Mid-Pyrennes	sandy clay loam	Central	Spain (Cataluna and Aragon)	FOCUS SW R4
Ireland	sandy clay loam	Central	UK (Northern Ireland)	None
Germany - Brandenburg	sandy silt loam	Central	Poland; Czech Republic	None
UK- Wales	clay loam	Central	None	None
UK- Cornwall & Devon	clay	Central	None	None
Finland - Etalae Suomi	sandy loam	Continental / Scandinavia	Sweden	FOCUS GW

The VetCalc tool addresses a wide variety of agricultural and environmental situations:

- Animal characteristics for major food-producing animals
- Associated manure characteristics
- Local agricultural practices
- Characteristics of the destination environment
- Fate and behaviour within three critical compartments

Background information on key drivers such as treatment regimes (both bodyweight and non-body-weight related), animal characteristics and husbandry practices, manure characteristics and management regimes, environmental characteristics (soil, hydrology, weather), agricultural practices and chemical parameters are provided within model databases.

Vetcalc can be split into four major modelling tasks:

- Provision of input on dosage regime and chemical characteristics

- Calculation of maximum/initial predicted environmental concentrations (PEC) in excreta and soil
- Simulation of subsequent fate in soil (including potential for run-off, leaching and degradation and estimation of PEC values in shallow groundwater)
- Simulation of subsequent fate in surface water (including potential for dilution/advection, degradation and partitioning and estimation of PEC values in the water column and sediment)

In order to carry out the required calculations three modelling components were developed:

- Graphic User Interface (including standardised regulatory calculations of PECexcreta and PEC_{soil})
- Modified LEACHP model: Simulation of fate in soil (including estimation of PECgroundwater)
- Fugacity model: Simulation of fate in surface waters (including estimation of PECsurface water)

The VetCalc model was designed to provide flexibility in the simulation of certain processes that may provide a degree of mitigation in more realistic exposure assessment, where warranted. As such, the model provides the user with the opportunity to define both a 'Basic' set of environmental fate and physico-chemical parameters for the compound under assessment (minimum dataset required at VICH Phase II) or an 'Advanced' option including opportunity to include:

- More accurate simulation of behaviour in water-sediment systems
- Metabolism
- Degradation during storage
- pH-dependant sorption
- Field dissipation versus lab degradation rates (influence of soil moisture and temperature conditions)
- Behaviour of metabolites

Using VetCalc

The programme can be downloaded from www.vmd.gov.uk 'go to downloads'.

A user manual is provided with VetCalc (accessed under 'View>User's manual') and this document should be consulted when running the software, in particular the tutorial in Chapter 9.

As discussed the VetCalc model consists of 12 exposure scenarios. For each of the scenarios there are at least two associated manure management systems. Within the manure management system there is the ability to select the time of year that spreading takes place and the duration of the storage period before spreading. The possibility exists of being able to run a large number of possible simulations. For this reason it is recommended that in the first instance for all types of MA application each of the 12 scenarios is run using the same basic parameters as described in the following paragraphs.

Vetcalc is set up by providing the required information through a number of input screens on the GUI.

Product label definition screen: which defines the target animal, the dose and duration of treatment and proportion of animals treated. These values are taken from the SPC.

Chemical properties 'Basic data' screen: which allows input of basic fate and physico-chemical data. Only enter a pKa if it is between 3 and 7 when the lowest K_{OC} value is used. When no pKa is entered use the average K_{OC}. The degradation half-life in soil is the average value. No data should be included on the 'Advanced Data' tab.

Simulation definition screen: Which defines the manure application parameters. 'Product usage' and 'animal characteristics' should be left as the default values for the selected animal type. In the manure management section for the scenario select the defaults as presented except for storage time which should be 365 days.

Scenario Characteristics screen: which defines the application date. Choose the suggested date for application of the manure.

Scenarios can be run individually or as a batch.

INTERPRETATION OF RESULTS FROM VETCALC

For VetCalc groundwater results are presented as annual average $PEC_{groundwater}$ values for a 10 year period and the 90^{th} percentile annual average value.

As for the FOCUS models, the VetCalc results for surface water are presented as the maximum predicted $PEC_{surfacewater}$ and the time of occurrence of the peak. The decline in concentrations after the peak is presented graphically.

GLOSSARY (DEFINITIONS OF TERMS)

Term		Definition
ADME	=	Absorption, Distribution, Metabolism, Excretion
ARs	=	Assessment Reports
ACR	=	Acute to Chronic Ratio
ASTM	=	American Society for Testing of Materials
BCF	=	Bioconcentration Factor
BMF	=	Biomagnification Factor
CVMP	=	Committee for Medicinal Products for Veterinary Use
DOTTS	=	Dung Organism Toxicity Testing Standardisation
EFSA	=	European Food Safety Authority
EMEA	=	European Medicines Agency
EIA	=	Environmental Impact Assessment
EIC	=	Environmental Introduction Concentration
EU		European Union
EUROSTAT	=	Statistical Office of the European Communities
EU TGD	=	Technical Guidance Document on Risk Assessment in support of the Commission Directive 93/67/EEC on risk assessment for new notified substances and Commission Regulation (EC) 1488/94 on risk assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council on placing Biocidal products on the market.
FOCUS	=	Forum for the Coordination of Pesticide Fate Models and Their Use
GMO	=	Genetically Modified Organisms
ISO/DIS	=	International Organisation for Standardisation/Draft International Standards
IOBC	=	International Organisation for Biological Control
MA	=	Marketing Authorisation
NOAEL	=	No-Observed-Adverse-Effect-Level
NOEC	=	No-observed effect concentration, i.e., the test concentration at which no adverse effect occurs
NSAIDS	=	Non-Steroidal Anti-Inflammatory Drugs
NOAEL	=	No-Observed-Adverse-Effect-Level
NTA	=	Notice to Applicants
OECD	=	Organization for Economic Co-operation and Development
PEC	=	Predicted Environmental Concentration
PNEC	=	Predicted No Effect Concentration
PBT	=	Persistent Bioaccumulative Toxic
QSAR	=	Quantitative Structure Activity Relationship
RIVM	=	The Dutch National Institute for Public Health and the Environment
RI	=	Reliability Index
RQ	=	Risk Quotient
SEPA	=	Scottish Environment Protection Agency
SPC	=	Summary of Product Characteristics
SSF	=	Species Sensitivity Factor
SETAC	=	Society of Environmental Toxicology and Chemistry
TME	=	Terrestrial Model Ecosystems
VICH	=	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products
VMP	=	Veterinary Medicinal Product