VICH International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

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# Guidance for Industry

## ENVIRONMENTAL IMPACT ASSESSMENTS (EIA's) FOR VETERINARY MEDICINAL PRODUCTS (VMP's) - PHASE II

## VICH GL38

## FINAL GUIDANCE

This VICH guidance document provides guidance for the use of a single set of environmental fate and toxicity data to be used by applicants/sponsors to obtain marketing approval in all VICH regions for those veterinary medicinal products (VMP's) identified as recommending data during the Phase I process.

Comments and suggestions regarding the document should be submitted to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments. All comments should be identified with the Docket No. 2004D-0156.

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**For implementation at Step 7**

# ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS

# PHASE II GUIDANCE

Recommended for Adoption
at Step 7 of the VICH Process
in October 2004 by the VICH SC for implementation in October 2005

This Guidance has been developed by the appropriate VICH Expert Working Group and is subject to consultation by the parties, in accordance with the VICH Process. At Step 7 of the Process the final draft was recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

# VICH-GL38
# ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS PHASE II GUIDANCE

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# ENVIRONMENTAL IMPACT ASSESSMENT FOR VETERINARY MEDICINAL PRODUCTS - PHASE II

***This guidance represents the Food and Drug Administration's (FDA's) current thinking on the subject matter. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.***

## 1 INTRODUCTION

### 1.1 Purpose of this Guidance Document

The purpose of this document is to provide guidance for the use of a single set of environmental fate and toxicity data to be used by applicants/sponsors to obtain marketing approval in all VICH regions for those veterinary medicinal products (VMPs) identified as recommending data during the Phase I process. It also aims to be a major contribution towards the common use of study methods used to generate these data.

It needs to be kept in mind that guidances should not consist of rigid stipulations, but should make clear recommendations on the minimum information needed. By their nature, guidances address most, but not all possible eventualities. Each case has to be considered on its merits, and if in a particular circumstance an alternative approach, for example use of data published in the literature, is deemed more fitting, a reasoned argument for the deviation should be prepared and discussed with appropriate regulatory authorities before work is initiated.

Besides serving as a common basis for the Environmental Impact Assessment (EIA), this document provides recommendations to protect the environment. The field of ecotoxicology is a complex science and gaps in data and knowledge exist. Notwithstanding these limitations, the Phase II recommendations should be based on science and strive for objectivity. The maximum amount of information should be extracted from each study to achieve an understanding of the potential for a given VMP to affect the environment.

An important factor in the use of the guidance contained herein is professional judgement. Expertise in the appropriate scientific disciplines is a valuable prerequisite for designing an EIA program for VMPs. Such expertise is important in evaluating the relevance of available data, for predicting environmental exposures, for identifying the recommended studies, and interpreting exposures relative to endpoint values obtained in such studies.

**FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.**

## 1.2 Scope

The mandate given by the VICH Steering Committee for developing this guidance is described in the Phase I document (http://www.emea.eu.int/pdfs/vet/vich/059298en.pdf, http://www.fda.gov/cvm/guidance/guide89.pdf).

The scope of the guidance is for VMPs, as defined by the individual parties to VICH. Particular VICH regions may mandate legislatively that this guidance be applicable to new products only or to both new and old products. Therefore, it is incumbent upon the applicant/sponsor to determine what the case is for a particular VMP. If an applicant/sponsor uses an alternative approach to conducting an EIA, then they should assess the suitability of the deviation from the guidance contained herein with the appropriate regulatory authority. However, an alternative approach, depending on the nature of the deviation from the guidance and the justification for it, may result in a submission not being accepted by all parties to VICH.

# 2 GENERAL ELEMENTS

Phase II provides a common basis for EIA testing for VMPs between the EU, Japan, US, Canada and Australia/New Zealand. It is recognized that significant regional differences (e.g. animal husbandry practices, climates, soil and water types, etc.) preclude fully harmonized guidance at this time. Full harmonization on principles of fate, effects and risk assessment is possible; the parameterization and decision making is, however, the prerogative of the individual regulatory authority. For this reason, the scope and extent of information recommended for EIAs for all regions cannot be completely specified. To the extent possible, Phase II provides recommendations for standard datasets and conditions for determining whether more information should be generated for a given VMP.

## 2.1 Protection Goals

Legislation and policy on environmental quality in the VICH regions set out the protection goals reflected in the EIA. The overall target of the assessment is the protection of ecosystems.

The aim of the guidance provided in Phase II (and in Phase I) is to assess the potential for VMPs to affect non-target species in the environment, including both aquatic and terrestrial species. It is not possible to evaluate the effects of VMPs on every species in the environment that may be exposed to the VMP following its administration to the target species. The taxonomic levels tested are intended to serve as surrogates or indicators for the range of species present in the environment.

Impacts of greatest potential concern are usually those at community and ecosystem function levels, with the aim being to protect most species. However, it may be important to distinguish between local and landscape effects. There may be some instances where the impact of a VMP at a single location may be of significant concern, for example, for endangered species or a species with key ecosystem functions. These issues should be handled by risk management at that specific location, which may even include restriction or prohibition of use of the product of concern in that specific local area. Additionally, issues associated with cumulative impact of some VMPs may be appropriate at a landscape level. These types of issues cannot be harmonized but should be considered as part of the EIA and if recommended, addressed by each region/local area.

## 2.2 General Description and Use of Phase II

This Phase II guidance contains sections for each of the major branches: (1) aquaculture, (2) intensively reared terrestrial animals and (3) pasture animals, each containing decision trees pertaining to the branch. The document also contains a section listing the recommended studies for

physical/chemical properties, environmental fate and environmental effects, as well as a description of how to determine when studies may be relevant.

The guidance uses a two-tiered approach to the environmental risk assessment. The first tier, Tier A, makes use of simpler, less expensive studies to produce a conservative assessment of risk based on exposure and effects in the environmental compartment of concern. If the EIA cannot be completed with such data, due to a prediction of unacceptable risk, then the applicant/sponsor progresses to Tier B to refine the EIA.

In some cases, it may be possible to implement a risk management option instead of moving to Tier B. In these cases, discussion with the regulatory authority is recommended. It should be recognized that risk management may not be identical for all regions and where Tier B testing is omitted in one region, it may still be recommended in another.

For certain VMPs, it may be recommended to go beyond Tier B because more complex studies, specific to issues being addressed or to a particular region, are recommended to complete the risk assessment. Such studies cannot be comprehensively dealt with in a harmonized guidance document. Therefore, these issues do not fall within the purview of this document, but should be addressed on a case-by-case basis with the appropriate regulatory authority. Examples include exceeding relevant trigger values in Tier B, where further testing may be warranted and/or risk mitigation measures may be recommended. As risk management measures are not within the scope of this guidance document, no guidance on these aspects is possible.

## 2.3 Exposure of VMPs to the Environment

The route and quantity of a VMP entering the environment determines the risk assessment scenarios that are applicable and the extent of the risk assessment. This guidance sets out a number of emission scenarios, using various assumptions. There may be some emission scenarios that are not applicable to a specific region. Emission can occur at various stages in the life cycle of the product. However, with the exception of certain topicals or those added directly to water, most VMPs first pass through the animal to which it is administered. Generally the most significant environmental exposure results from excretion of the active substance being the parent and/or its metabolites. Following excretion, residues are generally assumed to be uniformly distributed in the environment; even though distribution may be patchy.

## 2.4 Risk Quotient (RQ) Approach

The EIA is based on the accepted principle that risk is a product of the exposure, fate and effects assessments of the VMP for the environmental compartments of concern. The Phase II EIA is based on a RQ approach, which is the ratio of the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC) on non-target organisms. 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.

The PEC of the RQ is defined as the concentration of the parent compound and metabolites predicted to be present in the soil, water and sediment compartment. Worldwide harmonization of PEC calculations is not practical or possible at this time. Regional differences in animal husbandry practices, different environmental conditions in the VICH regions, differences in treatment rates and frequency, should be taken into account when calculating PECs. Therefore this document does not contain any examples of PEC calculations but gives some general qualitative guidance needed to determine PECs. It is incumbent upon the applicant/sponsor to determine the most appropriate

method of estimating exposures for the region of interest for a particular VMP based on regulatory guidance.

The PNEC of the RQ is determined from the experimentally determined effects endpoint divided by an appropriate assessment factor (AF). The AF is intended to cover uncertainties such as intra- and inter-laboratory and species variation, the need to extrapolate from laboratory study results to the field, and from short term to long term toxicity (acute:chronic ratios). The value varies depending on the type of study conducted. Variation in the AF applied should be clearly justified in the submission.

AFs of between 1000 and 10 are used in the assessment. A factor of 1000 is designed to be conservative and protective and is applied when only limited data are available; this value may be progressively reduced to 10 as more evidence becomes available. Such evidence could include:

(1) availability of data from a wide variety of species including those which are considered to represent the most sensitive species.

(2) information from structurally similar compounds, to suggest that the acute to chronic ratio is likely to be lower than that for many other compounds; and

(3) information to suggest that the chemical is rapidly degraded and not repeatedly administered so as to lead to chronic exposure.

## 2.5 Test Guidelines

The specific test guidelines/protocols recommended in Phase II are those finalized by OECD/ISO. This has the advantage of ensuring that environmental studies are current and broadly acceptable to regulatory authorities on a worldwide basis. Lack of a specific study recommendation, however, does not eliminate the importance for data on the specific organism class identified. In these situations, it is up to the applicant/sponsor to seek guidance from the appropriate regulatory authority.

Finally, conducting EIA studies in accordance with Good Laboratory Practice (GLP) is a regional requirement. It is preferred that studies should be conducted using methods that allow for a data audit as may be necessary for some regions. It should be recognized that if studies are not conducted to GLP, they may not be accepted in some VICH regions.

## 2.6 Metabolites

In triggering a Phase II assessment, the exposure is based on the total residue approach, as described in question 11 and 17 of the Phase I document. The fate of chemicals in the environment is dependent on their chemical/physical properties and degradability. These properties will vary between the parent compound and the individual excreted metabolites, for example, the latter may be more water-soluble than the parent compound and may be more mobile and/or more persistent in the environment.

In general, the data generated at Phase II will be on the parent compound, but the risk assessment should also consider relevant metabolites. This is especially the case for pro-drugs that are efficiently metabolized into a single metabolite for which testing may be more appropriate.

Consideration of the excretion data is not initially recommended at Tier A, where a total residue approach should be taken and a $PEC_{initial}$ should be estimated. It should be assumed that the VMP is excreted 100% as parent.

If the RQ is $\geq 1$ for one or more tested taxonomic levels, then metabolism/excretion data from the residues and ADME part of the dossier should be considered as part of the PEC refinement.

Excreted metabolites representing 10% or more of the administered dose and which do not form part of biochemical pathways should be added to the active substance to allow the PEC to be recalculated.

If the RQ is still ≥1 after PEC refinement and testing at Tier B, then guidance should be sought from the regulatory authority, including whether testing of the major environmentally relevant metabolites should be considered.

## 2.7 Special Consideration for Biodegradation Data

At Tier A if the RQ is <1 for all taxonomic levels tested, the assessment should normally stop. However, for persistent compounds (e.g. DT90 > 1 year in soil based on the annual appication) it is recommended that the PECinitial be recalculated due to the possibility of accumulation in the environment.

In case of specific concerns related to the persistence and/or mobility, further investigation of degradates formed during environmental fate studies may be important. It should be noted that an individual substance may be both an excreted metabolite and a degradate in the environment. In both cases guidance should be sought from the regulatory authority.

# 3 RECOMMENDED STUDIES AT TIER A AND TIER B

Exposure to both the terrestrial and aquatic compartment may be applicable to a particular VMP depending on its route of environmental introduction. For instance, VMPs administered to intensively reared animals have the potential to impact terrestrial non-target species directly and non-target species in surface waters indirectly due to transport in water, including when adsorbed to soil particles and organic matter. Likewise, VMPs used to treat pasture animals may impact aquatic as well as terrestrial non-target species. Therefore, there should be a common set of criteria and studies that will be used when it is determined that testing is recommended. These can be applicable to all three branches or just two, e.g. intensively reared and pasture animals and are cross-referenced (as appropriate) in later sections of this document. If there is evidence that there will be no exposure to a particular compartment (i.e. water, soil/sediment and dung), then it may be possible to waive studies for that compartment. However, sound scientific evidence should be presented in the dossier in support of the omission of these studies.

This section summarizes the studies that are recommended at Tier A, and which should be conducted once it has been determined at Phase I that testing at Phase II is recommended. It also outlines the process that should be followed to determine whether testing at Tier B may be relevant and lists the studies recommended at this level.

All testing should be carried out on the parent compound, with the possible exception of VMPs such as pro-drugs as already discussed in section 2.6.

## 3.1 Tier A Testing

### 3.1.1 Tier A Physical-Chemical Properties Studies

Table 1 gives the studies recommended in this area in Tier A for all three Branches. Except where noted, all studies should be conducted.

**Table 1. Physical-chemical Properties Studies at Tier A**

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

* Calculation only, though a study is recommended when other physical-chemical properties, e.g. molecular weight, melting temperature, thermogravimetric analysis suggest that the vapour pressure may exceed $10^{-5}$ Pa at 20°C.
** This criterion is not directly applicable to ionisable substances at environmental pH. If appropriate, the logKow for such substances should be measured on the non-ionised form at environmentally relevant pHs.

## 3.1.2 Tier A Environmental Fate Studies

Table 2 gives the recommended studies in this area in Tier A for all three branches. The degradation study should only be performed in soil or aquatic systems, depending on whether the initial exposure is to the terrestrial or aquatic environment. The photolysis and hydrolysis studies are optional (see comments under sections 4.2.1.2, 5.2.1.2 and 6.2.1.2) for the three branches.

**Table 2. Environmental fate studies at Tier A**

| Study | Guideline |
|---|---|
| Soil Adsorption/Desorption* | OECD 106 |
| Soil Biodegradation (route and rate)** | OECD 307 |
| Degradation in aquatic systems** | OECD 308 |
| Photolysis (optional) | Seek regulatory guidance*** |
| Hydrolysis (optional) | OECD 111 |

*Adsorption/desorption studies should report both the $K_{oc}$ and $K_d$ values for a range of soils. Care should be taken in extrapolating the study results from soil to sediment, especially for substances which are ionized at environmentally relevant pHs.
** These studies are recommended only for the terrestrial and aquaculture branches, respectively. It may be appropriate to do the latter studies under saltwater conditions (regulatory guidance should be sought).
*** Draft OECD test guidelines for both aquatic and soil photolysis are in preparation.

## 3.1.3 Tier A Effects Testing

### 3.1.3.1 Tier A Aquatic Effects Studies

Table 3 gives the studies and AFs recommended in Tier A for both direct and indirect aquatic exposures. Testing of three taxonomic levels is recommended. At least one fish, one aquatic invertebrate and one algal species should be tested and the PNEC estimates for all taxonomic levels used individually for the RQ calculations.

VMPs to be used in freshwater should be studied using fresh water species and under freshwater conditions. Those used in saltwater should be studied using saltwater species and under saltwater conditions. Only the freshwater studies should be conducted for VMPs used on terrestrial animals. Species used should be characteristic of the environmental conditions (temperature range especially) in the region of use.

**Table 3. Aquatic effects studies at Tier A**

| Medium | Studies | Toxicity endpoint | AF | Guideline |
|---|---|---|---|---|
| Freshwater | Algal growth inhibition* | $EC_{50}$ | 100 | OECD 201 |
| Freshwater | *Daphnia* immobilization | $EC_{50}$ | 1000 | OECD 202 |
| Freshwater | Fish acute toxicity | $LC_{50}$ | 1000 | OECD 203 |
| Saltwater | Algal growth inhibition | $EC_{50}$ | 100 | ISO 10253 |
| Saltwater | Crustacean acute toxicity | $EC_{50}$ | 1000 | ISO 14669 |
| Saltwater | Fish acute toxicity | $LC_{50}$ | 1000 | Seek regulatory guidance |

* For substances with anti-microbial activity, some regulatory authorities prefer a blue-green algae rather than a green algae species be tested.

### 3.1.3.2 Tier A Terrestrial Effects Studies

Table 4 gives the studies and AFs recommended in Tier A for soil exposures. These are generally only applicable to VMPs used for terrestrial treatments. All studies should be done and the PNEC estimates for all taxonomic levels used individually for the RQ calculations. 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).

In general, endo/ectoparasiticidal substances are not considered to be toxic for plants and microorganisms. Therefore for endo/ectoparasiticides used on pasture animals studies on plants and microorganisms are only recommended in case the trigger value given in Phase I is exceeded.

**Table 4. Terrestrial effects studies at Tier A**

| Study | Toxicity endpoint | AF | Guideline |
|---|---|---|---|
| Nitrogen Transformation (28 days)* | $\leq$ 25% of control | ** | OECD 216 |
| Terrestrial plants | $EC_{50}$ | 100 | OECD 208 |
| Earthworm Subacute/reproduction | NOEC | 10 | OECD 220 / 222 |

* Studies should be conducted at 1X and 10X the maximum PEC.

** An assessment factor is not relevant to this end point – when the difference in rates of nitrate formation between the lower treatment (i.e. the maximum PEC) and control is equal to or less than 25% at any sampling time before day 28, the

VMP can be evaluated as having no long term influence on nitrogen transformation in soils. If this is not the case, the study should be extended to 100 days at Tier B (see Table 8).

In the specific case of endo/ectoparasiticides used in pasture treatments, the studies listed in Table 5 are also recommended for dung exposures. Regulatory guidance should be sought to determine the appropriate test guidelines to be used to conduct the toxicity studies for dung fauna. Both dung beetle larval and dung fly larval data are recommended to assess the effects on dung fauna of endo/ectoparasiticides excreted in dung. Regulatory guidance should be sought to determine the appropriate study guidelines to be used to conduct the effects studies for dung fauna. If sound scientific reasons can be advanced, for example evidence of nil absorption for topicals or extensive excretion in the urine, then these studies may be waived.

**Table 5. Additional effects studies recommended for endo/ectoparasiticides used for pasture treatments at Tier A**

| Study | Toxicity endpoint | AF | Guideline |
|---|---|---|---|
| Dung fly larvae | $EC_{50}$ | 100 | Seek regulatory guidance* |
| Dung beetle larvae | $EC_{50}$ | 100 | Seek regulatory guidance* |

* There are currently no internationally accepted guidelines or processed drafts available for these studies, but the VICH WG noted the ongoing work in developing standardised studies for dung fly and dung beetle larvae and their inclusion into the OECD Test Guidelines Program.

Studies for toxicity to vertebrates (e.g. mammals and birds) are not recommended. However, there may be cases where there is both high toxicity and potential exposure through the food chain and a consequent risk. An example is risk to birds feeding on the backs of animals that have been treated with pour-on formulations of endo/ectoparasiticides with potentially high mammalian/avian toxicity. In these cases, the applicant should consider the mammalian and (if available) avian toxicity data and seek regulatory guidance as to whether additional data are recommended.

### 3.1.4 Risk assessment at Tier A

The risk assessment approach that is recommended is to compare the $PEC_{initial}$ based on the total residue with the PNEC derived for each of the tested taxonomic levels as described above. Where the RQ for all taxonomic levels is < 1 it should be sufficient to conclude that the VMP does not pose a risk for the environment, unless based on the persistence of the active substance there is a potential for it to accumulate in the environment (see section 2.7). Where the RQ is ≥ 1 a risk for the environment can not be excluded and further assessment is recommended.

#### 3.1.4.1 PEC refinement

The first step should be to refine the $PEC_{initial}$ based on the total residue at Tier A through consideration of the metabolism/excretion information and the data on biodegradation in manure/soil/aquatic systems data (see section 2.6 and 2.7). The $PEC_{refined}$ should then be compared with the PNEC for the affected taxonomic level and a new RQ determined for each. If the RQ is now <1 for all taxonomic levels, the assessment stops.

If the RQ is still ≥1 for any of the taxonomic levels tested, then the VMP moves to Tier B and testing for the affected taxonomic level is recommended.

For pasture treatments if the RQ is ≥1 for dung insects for the $PEC_{dung\text{-}initial}$, then the excretion data should be examined and the $PEC_{dung\text{-}refined}$ used to recalculate the RQ. The $PEC_{dung\text{-}initial}$ assumes that all of the dose is excreted in a single day's dung. The $PEC_{dung\text{-}refined}$ is more realistic as it takes account of how many days the active substance is excreted in dung and at what concentrations (see Section 6.2.3.3). If the RQ is still ≥1, further regulatory guidance should be sought.

## 3.2 Criteria for Tier B Testing

The main criteria for advancing to Tier B is when the RQ is ≥1 or in the case of soil micro-organisms an effect > 25%. Effects studies at Tier B are only recommended for affected taxonomic levels. There are two other cases relating to bioaccumulation and sediment invertebrate toxicity where Tier B testing is recommended.

The $logK_{ow}$ ≥4 is used as a criterion for an assessment of bioaccumulation. This criterion is not directly applicable to ionisable substances at environmental pH. If appropriate, the $logK_{ow}$ for such substances should be measured on the non-ionised form at environmentally relevant pHs.

If the RQ for aquatic invertebrate is ≥1 it is recommended to consider the $PEC_{sediment}/PNEC_{sediment}$ ratio. The $PNEC_{sediment}$ is calculated using equilibrium partitioning. This method uses the $PNEC_{aquatic\ invertebrate}$ and the sediment/water partitioning coefficient as input. If the RQ is ≥1, then testing of sediment organisms is recommended. For substances with a log $K_{ow}$ ≥5, the RQ is increased by an extra factor of 10 to take account of possible uptake via ingestion of sediment. If the RQ is ≥1, then a study, preferably long-term, with benthic organisms using spiked sediment is recommended.

## 3.3 Tier B Testing

### 3.3.1 Tier B Physical-Chemical Properties Studies

Usually, there are no additional physical-chemical studies recommended in Tier B.

### 3.3.2 Tier B Environmental Fate Studies

If the $logK_{ow}$ is ≥4, evidence from metabolism/residues/excretion, biodegradation studies and molecular mass should be considered to see whether there is the potential for bioaccumulation to occur. If so, then the study listed in Table 6 is recommended to be carried out at Tier B. To assess the risk for secondary poisoning, the use of a predicted BCF based on QSARs may be considered. If in doubt, regulatory guidance should be sought.

**Table 6. Environmental fate study at Tier B**

| **Study** | **Guideline** |
|---|---|
| Bioconcentration in fish | OECD 305 |

If the BCF is ≥1000, regulatory guidance should be sought.

### 3.3.3 Tier B Environmental Effects Studies

#### 3.3.3.1 Tier B Aquatic effects studies

The studies in Table 7 are recommended only for those cases where the RQ for the affected taxonomic level is ≥1 following use of the $PEC_{\mathbf{refined}}$ (see section 3.1.4).

**Table 7. Aquatic effects studies at Tier B**

| Environment | Study | Toxicity Endpoint | AF | Guideline |
|---|---|---|---|---|
| Freshwater | Algae growth inhibition* | NOEC | 10 | OECD 201 |
| Freshwater | *Daphnia magna* reproduction | NOEC | 10 | OECD 211 |
| Freshwater | Fish, early-life stage** | NOEC | 10 | OECD 210 |
| Freshwater | Sediment invertebrate species toxicity | NOEC | 10 | OECD 218, 219*** |
| Saltwater | Algae growth inhibition* | NOEC | 10 | ISO 10253 |
| Saltwater | Crustacean chronic toxicity or reproduction | NOEC | 10 | Seek regulatory guidance |
| Saltwater | Fish chronic toxicity | NOEC | 10 | Seek regulatory guidance |
| Saltwater | Sediment invertebrate species toxicity | NOEC | 10 | Seek regulatory guidance |

* Using the same study and species as in Tier A but the NOEC is used in Tier B.
** Alternative studies for fish: Fish short term toxicity test on embryo and sac-fry stage (OECD TG 212) and Fish juvenile growth test (OECD TG 215) are not favoured, noting *inter alia* that the first page of the former suggests why this may not be the first choice guideline and that OECD TG 210 is preferable.
*** It is suggested that if entry into the environment is through water, OECD TG 219 is used, if exposure is through sediment or adsorbed to soil in run-off, OECD TG 218 should be used.

If after the Tier B testing the RQ is $\geq$1, regulatory guidance should be sought.

### 3.3.3.2 Tier B Terrestrial effects studies

The studies in Table 8 are recommended only for those cases where the RQ for the affected taxonomic levels is ≥1 or in the case of soil micro-organisms an effect > 25% following use of the $PEC_{\mathbf{refined}}$ (see above).

**Table 8. Terrestrial effects studies at Tier B**

| Study | Endpoint | AF | Guideline |
|---|---|---|---|
| Nitrogen Transformation (100 days – extension of Tier A study) | ≤ 25% of control | * | OECD 216 |
| Terrestrial plants growth, more species** | NOEC | 10 | OECD 208 |
| Earthworm | | | None |

* An assessment factor is not relevant to this end point - when the difference in rates of nitrate formation between the lower treatment (i.e., the maximum PEC) and control is equal to or less than 25% at any sampling time before day 100, the VMP can be evaluated as having no long term influence on nitrogen transformation in soils.
** The study should be repeated on two additional species from the most sensitive species category in the Tier A study, in addition to repeating the study on the most sensitive species.

If after the Tier B testing the RQ is ≥1 or in the case of soil micro-organisms an effect > 25%, regulatory guidance should be sought.

For pasture treatments, if the RQ is still ≥1 for dung fauna from the $PEC_{dung\text{-}refined}$, no additional studies are recommended at Tier B, but regulatory guidance should be sought.

# 4 AQUACULTURE BRANCH

## 4.1 Introduction

This section of the Phase II guidance deals with the environmental risk assessments for VMPs used in aquaculture. A variety of VMPs are administered to aquatic organisms. In many cases these are added to the organism's food or directly to their water, or they may be injected directly into the organism.

Aquaculture practices may vary widely between the VICH regions, but the generic types of aquaculture facilities are:

- net pens and cages in ocean, coastal and inland areas such as bays, estuaries, fjords, lakes and lochs;
- raceways, ponds or tanks/baths taking from, and returning water to, streams or rivers;
- raceways, ponds or tanks/baths discharging to a sewage treatment facility; and
- isolated ponds or tanks with limited discharge to a river or sewage treatment facility.

The above give an indication of the spectrum of aquaculture facilities, which range from systems fully open to essentially closed to the aquatic environment. However, in the majority of cases there will be dilution of treated water/effluent on release into the environment.

Even with fully open systems during treatment with a VMP the net pen is often raised, e.g. so that the fish are contained in 2-3 m depth of water and enclosed in a tarpaulin to achieve the required concentration for a specified time period. At completion of the treatment, the used drug is assumed to be equally distributed within the reduced volume of water in the net pen. Following removal of the tarpaulin, the released active substance may initially be distributed evenly within an area of water around the facility. Eventually more widespread distribution in the environment of the active

substance may occur due to passive diffusion/current movement. In other cases release may be more direct as no impervious barrier will be in place, or the tarpaulin is placed as a skirt around the net pen so that the bottom is open.

For systems that are partially closed to the environment, at the end of the VMP treatment release of effluent to the environment will occur together with other untreated water from the aquaculture facility. Again there will initially be dilution in receiving waters for a limited distance, followed by more widespread distribution. In some cases, effluent will pass through a sewage treatment facility, where there is the opportunity for the active substance to be removed by adsorption/degradation, prior to discharge to surface waters.

A decision tree/flow diagram is presented in Figure 1 at the end of this section as an overview of the risk assessment process for various types of VMPs used in aquaculture. The diagram provides a summary of the text, which is intended as a quick reference to the recommendations. However, the diagram should always be referred to in conjunction with the main text.

## 4.2 Tier A

### 4.2.1 Data recommended in Tier A

If a VMP used in aquaculture has failed to meet Phase I criteria, the following is the minimum testing data set recommended to be conducted in Tier A.

#### 4.2.1.1 Physical-chemical properties studies

Table 1, Section 3.1.1 gives the studies recommended in Tier A. Except where noted, all studies should be conducted.

#### 4.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the studies recommended in this area in Tier A. The degradation study should only be performed in aquatic systems. If initial chemical studies indicate a potential for the active substance to photolyse or hydrolyse, then photolysis or hydrolysis studies may be conducted.

#### 4.2.1.3 Environmental effects studies

Table 3, Section 3.1.3.1 gives the studies and AFs recommended in Tier A. At least one species should be studied from each of the three taxonomic levels, i.e. fish, invertebrates and algae in the relevant medium (fresh or saltwater), and the PNEC to be used for the RQ estimated for each taxonomic level.

### 4.2.2 Calculation and comparison of $PEC_{surfacewater}$

#### 4.2.2.1 Calculation of $PEC_{surfacewater\text{-}initial}$ ($PEC_{sw\text{-}initial}$)

The initial risk assessment should be conducted for a $PEC_{sw\text{-}initial}$.

The calculation should be based on:

- the total amount of VMP used in the aquaculture system within the consecutive administration period for one treatment (see Glossary);
- the volume of the aquatic environment within a defined distance of the treatment area (e.g. net pens), which is determined by the typical facility for the species and the country/region where the VMP is to be used;

- the assumption that the active substance is diluted within the system (the extent of which is dependent on the aquaculture practices and the facility and how it is operated), and then introduced into the wider environment;
- for a partially closed system, the extent of dilution within the fish farm and how much further dilution occurs in receiving waters such as running river/stream water when effluent is discharged from the fish farm; and
- for an open system, the extent of dilution is dependent on the shape, width and depth of the cultured area and water movement.

#### 4.2.2.2 Comparison of PNEC and $PEC_{sw\text{-}initial}$

At this stage, the PNEC for all taxonomic levels determined during aquatic effects testing should be compared with the $PEC_{sw\text{-}initial}$. If the RQ is <1 for all taxonomic levels, no further assessment is recommended. However, if the RQ is ≥1, the $PEC_{sw\text{-}initial}$ should be refined, using a number of mitigations as described in Section 4.2.2.3.

#### 4.2.2.3 Calculation of $PEC_{sw\text{-}refined}$

The $PEC_{sw\text{-}initial}$ calculations assume that all of the active substance is retained within the facility until released, and then is diluted only within a defined distance. The effect of further dispersal in open systems should be considered. Dispersal may be influenced by external factors such as wind, currents, tide and the extent of mixing of water as affected by temperature or salinity. The effect of adsorption onto sediments should be considered. There may also be a number of discrete applications within the one treatment period, which in open systems would be released as a series of pulses that will have largely dispersed prior to the next application.

### 4.2.3 Calculation and comparison of $PEC_{sediment}$

#### 4.2.3.1 Calculation of $PEC_{sediment}$

If the RQ for the aquatic invertebrate study is still ≥1 following the calculation of $PEC_{sw\text{-}refined}$, the $PEC_{sediment}$ should be calculated to compare with the $PNEC_{sediment}$ (see section 3.2) to indicate whether an effects study for sediment species is triggered and should be conducted at Tier B. As for $PEC_{surfacewater}$, this should initially be carried out at a basic level, and then further refined if necessary. At the basic level $PEC_{sediment\text{-}initial}$, it should be assumed that partitioning processes between sediment and water are complete, and that sediment and water are in equilibrium in the aquatic environment.

#### 4.2.3.2 Calculation of $PEC_{sediment}$ in cases of VMPs added to feed

It is often convenient to administer VMPs in the fish feed, particularly where a treatment has to be given for several days in succession. In such systems, the VMP may remain associated with waste feed which usually settles to the sediment under the net pens and for a distance beyond the net pens. For such VMPs it is also appropriate to calculate the $PEC_{sediment}$, using the following parameters:

- Percentage administered feed not eaten by fish and subsequently deposited on sediment;
- Total amount of VMP in fish feed;
- Percentage of dose excreted in faeces (in absence of data to the contrary assume this is 100% minus the percentage of uneaten feed);
- Area of sediment directly beneath the net pen(s) and distance beyond net pen(s) in which uneaten feed and faeces are deposited;

- Depth to which the active substance is distributed in sediment; and
- Density of sediment.

Therefore, the concentration of the active substance in the sediment is a function of the amount reaching sediment in uneaten feed, the amount reaching sediment in excreted faeces and the weight/volume of sediment in which the active substance is distributed.

#### 4.2.3.3. Comparison of PNEC and PEC

Once the $PEC_{sediment}$ has been calculated, it should be compared with the $PNEC_{sediment}$ as described in Section 4.2.3.1 to indicate whether an effects study for sediment species is triggered and should be conducted at Tier B.

## 4.3 Tier B

### 4.3.1 Triggers for testing in Tier B

The criteria for further testing at Tier B are given in Section 3.2.

### 4.3.2 Data recommended in Tier B

#### 4.3.2.1 Physical-chemical properties studies

Usually, there are no additional physical-chemical studies recommended in Tier B.

#### 4.3.2.2 Environmental fate studies

As noted in Section 3.3.2, if the $logK_{ow}$ is ≥4, and following the consideration given in that section, the bioconcentration study in fish listed in Table 6 is recommended for VMPs used in aquaculture at Tier B.

#### 4.3.2.3 Environmental effects studies

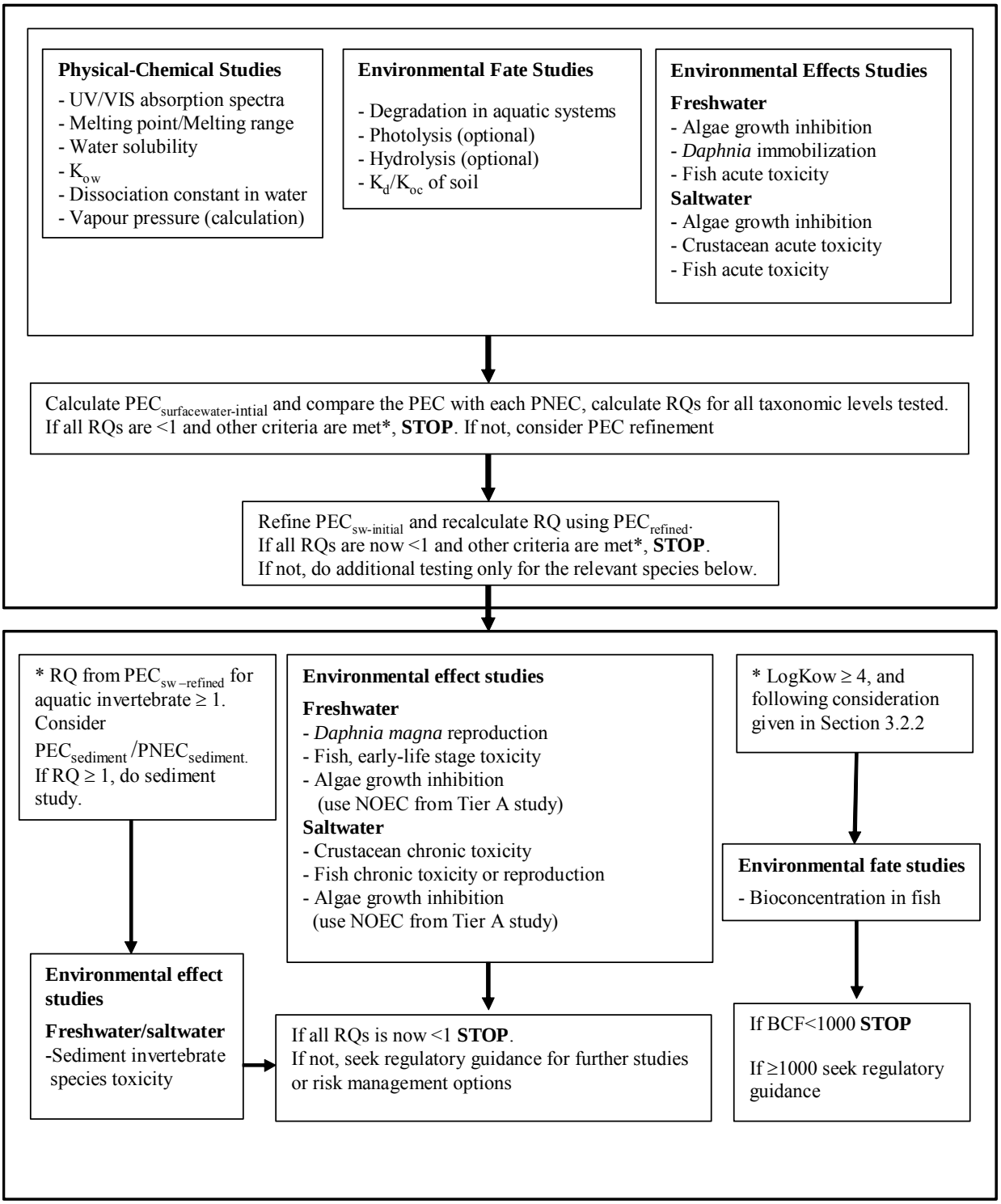
If the RQ is still ≥1 for one or more aquatic taxonomic levels, when the $PEC_{sw\text{-}refined}$ is compared with the PNECs calculated for the acute studies conducted in Tier A, chronic testing for that particular taxonomic level is recommended as indicated in Table 7 of Section 3.3.3.1.

If following refinement, the RQ for an aquatic invertebrate in surface water is ≥1, the $PEC_{sediment\text{-}refined}/PNEC_{sediment}$ should be considered. If RQ is ≥1, a sediment invertebrate effects study is recommended in Tier B.

### 4.3.3 Further assessment

If there is still an indication of risk on completion of the Tier B assessment, e.g. for VMPs which still have an RQ ≥1 or the BCF ≥ 1000, then the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority.

**Figure 1. Decision tree/Flow diagram for VMPs used for aquaculture**



# 5 INTENSIVELY REARED ANIMALS BRANCH

## 5.1 Introduction

This section of the Phase II guidance deals with the risk assessments for VMPs used in intensively reared animal systems.

Intensively reared animal systems consist of areas where animals are kept and raised in confined situations, which may include housed animals or animals kept in feedlots. Producers confine animals, feed, manure and urine in a relatively small land area (feed-yard). Feed is brought to the animals rather than the animals only grazing or otherwise seeking feed in pastures, fields, or on rangelands. Waste is usually disposed of off-site by spreading on adjacent fields. Facilities that have feedlots with constructed floors, such as solid concrete or metal slots would be considered intensive rearing practices. If a facility maintains animals in an area without vegetation, including dirt lots, the facility would also be considered an intensive animal feeding operation. Feedlots with nominal vegetative growth along the edges while animals are present or during months when animals are kept elsewhere are also considered to be intensive rearing operations. Beef cattle, dairy cattle, pigs, chickens, and turkeys are examples of species that may be reared in an intensive terrestrial system.

A decision tree/flow diagram is presented in Figure 2 at the end of this section as an overview of the risk assessment process for various types of VMPs used in intensively reared animals. The diagram provides a summary of the text, which is intended as a quick reference to the recommendations. However, the diagram should always be referred to in conjunction with the main text.

## 5.2 Tier A

### 5.2.1 Data recommended in Tier A

If a VMP used in intensively reared animal systems has failed to meet Phase I criteria, the following is the minimum testing data set recommended to be conducted in Tier A.

#### 5.2.1.1 Physical-chemical properties studies

Table 1, Section 3.1.1 gives the studies recommended in Tier A. Except where noted, all studies should be conducted.

#### 5.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the studies recommended in Tier A. For VMPs used in intensively reared animal systems the biodegradation study should be conducted only in soil. If initial chemical studies indicate a potential for the active substance to photolyse or hydrolyse, then photolysis or hydrolysis studies may be conducted.

#### 5.2.1.3 Environmental effects studies

Table 3, Section 3.1.3.1 gives the aquatic effects studies and AFs recommended in Tier A. For VMPs administered to intensively reared animals at least one species should be tested from each of the three taxonomic levels e.g. fish, invertebrates and algae, and the PNEC is estimated for each taxonomic level to be used for the RQ.

Table 4, Section 3.1.3.2 gives the terrestrial effects studies and AFs recommended in Tier A. The studies provide data on the potential effects to organisms representing three environmental

taxonomic levels in the terrestrial environment that are expected to be exposed, e.g. invertebrates, plants, and micro-organisms. Again the PNEC estimated for each taxonomic level is to be used for the RQ.

### 5.2.2 Calculation and comparison of $PEC_{soil}$

PECs of residues introduced to soil as a result of use of VMPs in the intensively reared animal systems are usually based on:

- The total amount of product administered; its dose and frequency of use per animal and pattern of use within a flock or herd;
- Metabolism in the treated animal, together with the pattern of excretion of parent and relevant metabolites;
- The manure output of the animal on a weight basis;
- Animal husbandry with respect to the number of animal cycles, length of individual animal cycles and proportion of year animals are housed;
- Manure storage times in relation to product usage; and
- Manure spreading practices in relation to any restrictions on time of spreading, whether manure is spread on an area once a year or on several occasions during the year, and legal or advisory limits to amounts spread.

#### 5.2.2.1 Calculation of $PEC_{soil\text{-}initial}$

In Phase II Tier A the $PEC_{soil\text{-}initial}$ is first calculated and used in the risk assessment. As noted in Section 2.6 this will assume 100% excretion of the administered dose as parent and will have been calculated as part of the Phase I assessment.

$PEC_{soil\text{-}initial}$ should give consideration under spreading practices to the possibility of repeat applications of manure containing a active substance to the same area of land. As noted in Section 2.7, this will be of particular concern for persistent compounds, where repeat applications over several years could lead to elevated soil concentrations with consequent effects on soil function and possibly other environmental impacts.

#### 5.2.2.2 Comparison of PNEC and $PEC_{soil\text{-}initial}$

At Tier A, the PNEC for all the taxonomic levels determined during terrestrial effects testing should be compared with the $PEC_{soil\text{-}initial}$. If the RQ is <1 for all taxonomic levels tested no further assessment is recommended. However, if the RQ is ≥1 for one or more taxonomic levels, the worst case $PEC_{soil\text{-}initial}$ should be refined, as described in Section 5.2.2.3, and the RQ recalculated.

#### 5.2.2.3 Calculation of $PEC_{soil\text{-}refined}$

The refinement of $PEC_{soil}$ should occur prior to consideration of conducting any testing in Tier B. Any refinement should be carried out using appropriate calculations and methods.

$PEC_{soil\text{-}initial}$ can be refined by determining the actual composition of the dose excreted by the treated animal. As noted in Section 2.6, where excretion data are available then the active substance and relevant metabolites (defined as representing 10% or more of the administered dose and which do not form part of biochemical pathways) should be added to allow an estimate of the $PEC_{soil\text{-}refined}$.

The PEC may be refined further by several adjustments, including but not limited to the following:

- accounting for any degradation of the active substance during storage of manure before spreading on fields, as appropriate; and
- by degradation of the parent and relevant metabolites in the field, using the results of the laboratory soil degradation study from Tier A. Time to mineralization, formation of bound residue or degradation to substances that are part of biochemical pathways can be used to refine the PEC in this case.

### 5.2.3 Calculation and comparison of PEC water

As noted in the introduction to section 3, VMPs administered to intensively reared animals have the potential to impact non-target species in surface waters indirectly due to transport in water, including when adsorbed to soils. Therefore, it is appropriate to calculate PECs for both surface and groundwater.

#### 5.2.3.1 Calculation and comparison of $PEC_{sw\text{-}initial}$

$PEC_{sw\text{-}initial}$ will be calculated from any form of indirect entry into surface water. $PEC_{sw\text{-}initial}$ is calculated from the $PEC_{soil\text{-}initial}$.

The factors that affect the likelihood of movement to surface water include the physical and chemical properties of the active substance, the amount of rainfall and the proportion that is likely to run off, and soil hydrology.

The PNEC for all tested aquatic taxonomic levels should be determined and compared with the $PEC_{sw\text{-}initial}$. If the RQ is <1 for all taxonomic levels, no further assessment is recommended. However, if the RQ is ≥1 for one or more taxonomic levels, the $PEC_{sw\text{-}initial}$ should be refined, using a number of mitigations as described in Section 5.2.2.3, and the RQ recalculated.

#### 5.2.3.2 Calculation of $PEC_{groundwater}$

The factors important in movement to groundwater include the physical and chemical properties of the active substance, the amount of soil organic matter, amount of rain, depth to the aquifer or seasonally saturated layer and preferential flow.

The $PEC_{groundwater}$ should be considered on a regional level for additional testing and/or mitigation for public health concerns. Groundwater is a natural resource and should not only be assessed with regards to public health but also to possible harmful effects to the biota of groundwater.

## 5.3 Tier B

### 5.3.1 Triggers for further testing in Tier B

The criteria for further testing at Tier B are given in Section 3.2.

### 5.3.2 Data recommended in Tier B

#### 5.3.2.1 Physical-chemical properties studies

Usually, there are no additional physical-chemical studies recommended in Tier B.

#### 5.3.2.2 Environmental fate studies

If the $\log K_{ow}$ is ≥4, and following the consideration given in Section 3.3.2, the bioconcentration study in fish listed in Table 6 is recommended for VMPs at Tier B.

#### 5.3.2.3 Environmental effects studies

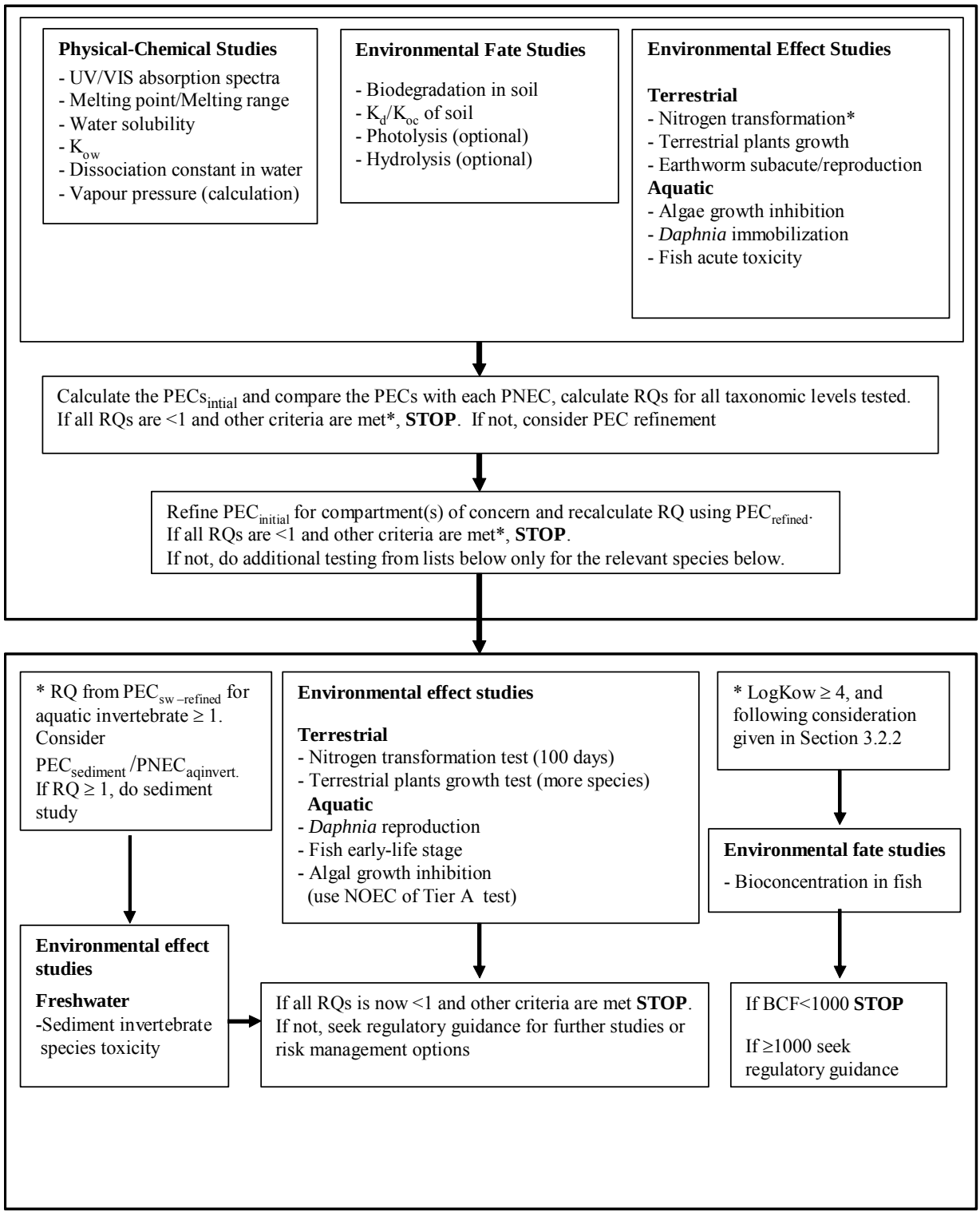
If the RQ is still ≥1 or in case micro-organisms an effect > 25% for one or more taxonomic levels (both aquatic or terrestrial) when the $PEC_{soil/sw\text{-}refined}$ is compared with the results of the studies conducted in Tier A, testing for that particular taxonomic levels should be carried out as indicated in Tables 7 and 8 of Section 3.3.3.

If following refinement, the RQ for an aquatic invertebrate in surface water is ≥1, the $PEC_{sediment\text{-}refined}/PNEC_{sediment}$ should be considered. If RQ is ≥1, a sediment invertebrate effects study is recommended in Tier B. For calculation $PEC_{sediment}$ see section 4.2.3.1.

### 5.3.3 Further assessment

If there is still an indication of risk on completion of the Tier B assessment, e.g. for VMPs which still have an RQ ≥1 or BCF ≥1000, then the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority.

**Figure 2. Decision tree/Flow diagram for VMPs used for intensively-reared animal systems**



# 6 PASTURE ANIMALS BRANCH

## 6.1 Introduction

This section of the Phase II guidance deals with the environmental risk assessment for VMPs used in animals kept at pasture.

Pasture is defined as land covered with grass or herbage and grazed by or suitable for grazing by livestock. Pasture animals are those livestock reared for part or all of the year on grassland, and refers only to the time spent at pasture. Excretion occurs directly onto the pasture or onto other habitats within the grazed area. This is in contrast to intensive systems such as feedlots where manure is collected and later spread onto agricultural or grassland. At pasture, grazing provides the primary source of food for livestock.

The types of pasture where animals are grazed will vary according to their situation within a region, for instance in different parts of the EU, and also between regions, e.g. there will be differences between Japan and Australia. The number of animals that can be maintained on an area of land will be limited; and the number of animals/hectare is referred to as the stocking density that will vary both within and between regions.

For animals reared on pasture, there are specific concerns for certain types of products related to their direct entry to the aquatic environment. There are also some specific areas of environmental concern relating to endo/ectoparasiticides used in animals at pasture and both of these are described in this guidance.

A decision tree/flow diagram is presented in Figure 3 at the end of this section as an overview of the risk assessment process for various types of VMPs used in pasture animals. The diagram provides a summary of the text, which is intended as a quick reference to the recommendations. However, the diagram should always be referred to in conjunction with the main text.

## 6.2 Tier A

### 6.2.1 Data recommended in Tier A

If a VMP used on pasture animals has failed to meet Phase I criteria, the following is the minimum testing data set recommended to be conducted in Tier A.

#### 6.2.1.1 Physical-chemical properties studies

Table 1, Section 3.1.1 gives the studies recommended in Tier A. Except where noted, all studies should be conducted.

#### 6.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the studies recommended in this area in Tier A. For pasture animal VMPs the biodegradation study should be conducted only in soil. If initial chemical studies indicate a potential for the active substance to photolyse or hydrolyse, then photolysis or hydrolysis studies may be conducted.

#### 6.2.1.3 Environmental effects studies

Table 3, Section 3.1.3.1 gives the aquatic effects studies and AFs recommended in Tier A. For VMPs administered to pasture animals at least one species should be tested from each of the three

taxonomic levels i.e. fish, invertebrates and algae, and the PNEC estimated for each taxonomic level is to be used for the RQ calculations.

Table 4, Section 3.1.3.2 gives the terrestrial effects studies and AFs recommended in Tier A. The studies provide data on the potential effects to organisms representing three environmental taxonomic levels in the terrestrial environment that are expected to be exposed, e.g. invertebrates, plants, and micro-organisms. However, for endo/ectoparasiticides used on pasture animals studies on plants and microorganisms are usually recommended only in the case the trigger value given in Phase I is exceeded. If data are available to show a concern for these taxonomic levels the studies are recommended. Again the PNEC estimated for each taxonomic level is to be used for the RQ calculations.

Both dung beetle larval and dung fly larval data are recommended to assess the effects on dung fauna of endo/ectoparasiticides excreted in dung. Regulatory guidance should be sought on the appropriate study guidelines to use to assess toxicity to dung fauna. An earthworm study, listed in Table 4, is also recommended in regions where dung is colonised by earthworms.

## 6.2.2 Calculation and comparison of $PEC_{soil}$

VMPs may be used on animals that are kept at pasture, rather than being housed or kept in feedlots. Consequently, any excretion of the active substance in urine or faeces will occur at pasture, rather than being collected, stored and spread onto land as manure. The proportion of the year livestock spend on pasture, in relation to the timing of treatment, is an important consideration when calculating the range of PEC values.

### 6.2.2.1 Calculation of $PEC_{soil\text{-}initial}$

At Tier A, an initial calculation of $PEC_{soil\text{-}initial}$ is recommended for all VMPs used in pasture animals, including topical products that are absorbed and excreted. Even though a later calculation will be done for $PEC_{dung\text{-}initial}$, at this stage the worst case calculation of $PEC_{soil\text{-}initial}$ should take account of active substance excreted in both faeces and urine. While in general, there will be excretion data available to determine the percentage of the administered dose of VMP excreted, and the relative contribution of parent and metabolites, initially it should be assumed that 100% of the administered dose is excreted onto pasture.

The $PEC_{soil\text{-}initial}$ is based on:

- 100% excretion of the administered dose;
- an assumption regarding depth of soil to which residue is distributed;
- livestock stocking density; and
- an even distribution of the active substance across the field.

### 6.2.2.2 Comparison of PNEC with $PEC_{soil\text{-}initial}$

At this stage, the PNECs for all taxonomic levels determined from terrestrial effects testing should be compared with the $PEC_{soil\text{-}initial}$. If the RQ is <1 for all taxonomic levels tested no further assessment is recommended. However, if the RQ is ≥1, the $PEC_{soil\text{-}initial}$ should be refined, using a number of mitigations as described in Section 6.2.2.3, and the RQ recalculated.

### 6.2.2.3 Calculation of $PEC_{soil\text{-}refined}$

The refinement of $PEC_{soil}$ should occur prior to consideration of conducting any testing in Tier B. Any refinement should be carried out using appropriate calculations and methods. Further

refinement of $PEC_{soil}$ can be done as described in Section 5.2.2.3 of the Intensively Reared Animals Branch.

## 6.2.3 Calculation and comparison of $PEC_{dung}$

### 6.2.3.1 Calculation of $PEC_{dung\text{-}initial}$

Some VMPs are excreted predominantly in the dung rather than in urine. Where such VMPs remain associated with the dung they are unlikely to be distributed in the soil initially, though there may be subsequent incorporation into soil by dung/soil fauna or by leaching.

For active substances excreted predominantly in dung, the $PEC_{dung\text{-}initial}$ should be estimated. This is the maximum concentration of the active substance in dung, and initially it should be assumed that there are no excretion data of the active substance in dung. Therefore, the $PEC_{dung\text{-}initial}$ should be calculated assuming that 100% of the dose is excreted in dung on a single day.

This is relevant in particular to endoparasiticides and ectoparasiticides that will be excreted at pasture following oral, parenteral or topical administration. For these products, the $PEC_{soil\text{-}initial}$ should also be estimated. However, there is also a need to estimate the concentration in dung as these products have the potential to affect dung fauna.

### 6.2.3.2 Comparison of PNEC with $PEC_{dung\text{-}initial}$

At this stage, the PNECs derived for dung fly, dung beetles and if applicable for earthworms should be compared with the $PEC_{dung\text{-}initial}$. If the RQ is <1 for all taxonomic levels tested no further assessment is recommended. However, if the RQ is ≥1, the $PEC_{dung\text{-}initial}$ should be refined, as described in Section 6.2.3.3, and the RQ recalculated.

### 6.2.3.3 Calculation of $PEC_{dung\text{-}refined}$

In Tier B, the concentration in dung, $PEC_{dung}$, is not expressed as a single value. Excretion studies may be used to produce more realistic estimates of the $PEC_{dung}$. Data should be obtained on the concentrations of active substance in fresh dung excreted by treated animals. Dung concentrations should be measured by an appropriate method and for a period adequate to determine the concentrations of ecotoxicological significance.

The maximum PEC in dung excreted at each time point is compared to the PNEC for dung fauna. An assessment can then be made of the time period after treatment during which dung is toxic to dung fauna.

## 6.2.4 Calculation and comparison of PEC water

### 6.2.4.1 Surface water and groundwater

VMPs administered to pasture animals have the potential to impact non-target species in surface waters indirectly due to transport in water, including when adsorbed to soils. Therefore it is appropriate to calculate PECs for both surface and groundwater (see Section 5.2.3 of this guidance). However, the $PEC_{groundwater}$ should be considered at a regional level.

In addition there are other routes of exposure to the aquatic environment that are specific to animals reared at pasture. These are described in Section 6.2.4.2 and should also be referred to.

### 6.2.4.2 Aquatic Exposure Scenarios

There are a number of ways that contamination of the aquatic environment may occur and more than one of the scenarios below may be relevant to an individual product. Therefore it may be

appropriate to add the PEC values from the different routes of exposure to arrive at a $PEC_{total}$. Alternatively the different routes of exposure may mean that contamination of surface water occurs over a longer period of time. These factors should be considered when estimating the $PEC_{sw\text{-}initial}$.

An initial risk assessment can be conducted at Tier A using the $PEC_{sw\text{-}initial}$ based on the concentration estimated in the scenarios below.

#### *6.2.4.2.1 Direct excretion of active substance into surface waters from pasture animals*

This is relevant in pasture situations where livestock have direct access to surface waters as a source of drinking water. In addition, it is only relevant to those livestock species, e.g. cattle, that spend time standing in the water.

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

This exposure scenario applies in situations where animals are gathered together in a specific area of the farm for application of topical ectoparasiticides. This may be an area of pasture, an area of bare ground, or an area of concrete. Such areas will become contaminated with VMPs as a result of mixing concentrate, splashing during administration, or from excess liquid draining from animals. During subsequent rainfall events there is potential for surface run-off of the active substance from this area to surrounding soil and nearby surface waters.

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

Animals treated with high volume VMPs include those that have been dipped, jetted or showered. After a period of time to allow excess liquid to drain off, treated animals will be returned to pasture. If they enter surface waters before the active substance has dried and adsorbed onto the greasy part of the fleece or hide, it will be readily lost into surface waters where the treated part of the body comes into direct contact with water. This will generally involve shallow surface waters and it may only be the legs, and possibly also the underbelly, that come into contact with water.

In general, animals that have been treated with a pour-on product (i.e., low volume) will not contaminate surface waters in this way, due to the low volumes used and the area of the animal to which the product is applied.

#### *6.2.4.2.4 Use and disposal of sheep dip*

Disposal of dilute dip to vegetated areas will lead to exposure of the soil and associated vegetation, as well as groundwater. High volume disposal of ectoparasiticides to land represents a potential impact in the environment and risk management may be important[1] to prevent this impact. Where this practice is allowed, data should enable an assessment of the risk to the environment to be performed, as part of the authorization process for these VMPs. These situations should be addressed by the applicant in consultation with the appropriate regulatory authority on a case-by-case basis.

1 This guidance document, developed under the VICH process, has been revised to conform to FDA's good guidance practices regulation (21 CFR 10.115).

#### *6.2.4.2.5 Sheep wool processing effluent*

This issue is a concern for certain regions, but not for all regions that are party to VICH. Therefore, this issue will not form part of this guidance document. Applicants should approach the relevant regulatory authority for guidance.

### 6.2.4.3 Comparison of PNEC with $PEC_{sw\text{-}initial}$

The PNECs for all the taxonomic levels determined during the aquatic effects testing should be compared with the $PEC_{sw\text{-}initial}$. If the RQ is <1 no further assessment is recommended. However, if the RQ is ≥1, the $PEC_{sw\text{-}initial}$ should be refined, as described in Section 6.2.4.4, and the RQ recalculated.

### 6.2.4.4 Calculation of $PEC_{sw\text{-}initial\text{-}refined}$

For $PEC_{sw\text{-}initial}$ it would be more realistic to assume that there is dilution and dispersion following entry into surface waters and there is the option to revise the $PEC_{sw\text{-}refined}$ in this way if the RQ are ≥1 for any aquatic taxonomic level. This should take account of the volume of the receiving water and the water flow-rate to estimate the extent of dispersion and dilution. The resulting $PEC_{sw\text{-}refined}$ will be lower, due to degradation, dilution, adsorption and dispersion, but will cover a larger area. Estimates should be made of the area affected and the resulting concentration. These estimates will tend to be region specific and advice may be sought from the regulatory authority. However, they are only empirical models at this stage, based on simple estimates, which can be refined later if necessary.

## 6.3 Tier B

### 6.3.1 Triggers for further testing in Tier B

The criteria for further testing at Tier B are given in Section 3.2.

### 6.3.2 Data recommended for Tier B

#### 6.3.2.1 Physical-chemical properties studies

Usually, there are no additional physical-chemical studies recommended in Tier B.

#### 6.3.2.2 Environmental fate studies

If the $\log K_{ow}$ is ≥4, and following the consideration given in Section 3.3.2, the bioconcentration study in fish listed in Table 6 is recommended for VMPs at Tier B.

#### 6.3.2.3 Environmental effects studies

If following refinement of the PECs the RQ is still ≥1 for one or more taxonomic levels (both aquatic or standard terrestrial) when the $PEC_{soil/sw\text{-}refined}$ is compared with the PNEC derived from Tier A or in case of micro-organisms an effect > 25%, additional testing for the particular taxonomic levels should be carried out as indicated in Tables 7 and 8 of Section 3.3.3.

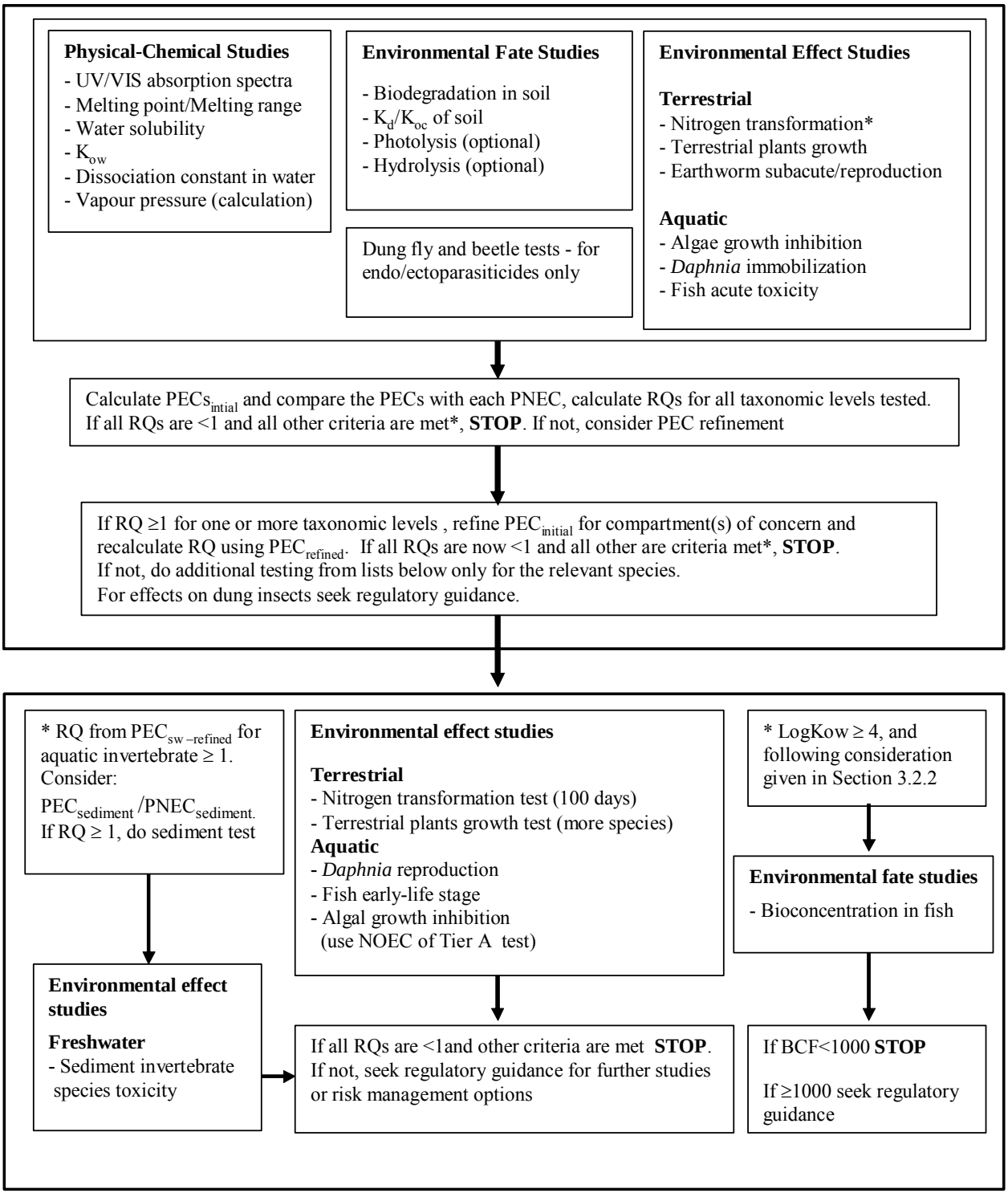
For the studies on dung fauna, if the RQs at Tier B, i.e. comparison of $PEC_{dung\text{-}refined}$ and PNEC, are still ≥1 for one or more taxonomic levels, then further testing should be conducted to determine the risk. Regulatory guidance should be sought on appropriate studies.

If following refinement, the RQ for an aquatic invertebrate in surface water is ≥1, the $PEC_{sediment\text{-}refined}/PNEC_{sediment}$ should be considered. If RQ is ≥1, a sediment invertebrate effects study is recommended in Tier B. For calculation $PEC_{sediment}$ see section 4.2.3.1.

### 6.3.3 Further assessment

If there is still an indication of risk on completion of the Tier B assessment, e.g. for VMPs which still have an RQ ≥1 or BCF ≥ 1000, then the applicant is recommended to discuss their dossier and proposals for further data or risk mitigation with the regulatory authority.

**Figure 3. Decision tree/Flow diagram for VMPs used for pasture animals**



# 7 GLOSSARY (DEFINITIONS OF TERMS)

| | | |
|---|---|---|
| Active substance | = | parent and/or its metabolites |
| ADME | = | Absorption, Distribution, Metabolism, Excretion |
| BCF | = | Bioconcentration Factor |
| $DT_{90}$ | = | Time to degradation of 90% of original concentration of the compound in the tested soils. |
| $EC_{50}$ | = | The concentration of a test substance which results in 50% of the test animals being adversely affected, i.e., both mortality and sub-lethal effects. |
| $K_d$ | = | Sorption/desorption coefficient |
| $K_{oc}$ | = | Sorption/desorption coefficient, normalized to organic carbon content |
| $K_{ow}$ | = | n-Octanol/water partitioning coefficient |
| $_{LC50}$ | = | The concentration of a test substance which results in a 50% mortality of the test species. |
| NOEC | = | No-observed effect concentration, i.e., the test concentration at which no adverse effect occurs. |
| OECD | = | Organization for Economic Co-operation and Development |
| One treatment | = | is considered to be administration of the VMP in accordance with the proposed marketing authorisation/registration, taking into account indication, amount administered and method of administration. A treatment can consist of multiple applications (e.g. once a day for seven consecutive days). |
| QSAR | = | Quantitative Structure Activity Relationship |

# 8 OECD/ISO TEST GUIDELINES FOR RECOMMENDED STUDIES

**OECD Guidelines for the Testing of Chemicals**
(http://www.oecd.org/en/home/0,,en-home-524-nodirectorate-no-no-no-8,00.html)

## Section 1 – OECD Physical-Chemical Properties

**ADOPTED TEST GUIDELINES**

| TG No. | Title |
|---|---|
| **101** | UV-VIS Absorption Spectra *(Original Guideline, adopted 12th May 1981)* |
| **102** | Melting Point/Melting Range *(Updated Guideline, adopted 27th July 1995)* |
| **104** | Vapour Pressure *(Updated Guideline, adopted 27th July 1995)* |
| **105** | Water Solubility *(Updated Guideline, adopted 27th July 1995)* |
| **106** | Adsorption/Desorption Using a Batch Equilibrium Method *(Updated Guideline, adopted 21st January 2000)* |
| **107** | Partition Coefficient (n-octanol/water): Shake Flask Method *(Updated Guideline, adopted 27th July 1995)* |
| **111** | Hydrolysis as a Function of pH *(Original Guideline, adopted 12th May 1981)* |
| **112** | Dissociation Constants in Water *(Original Guideline, adopted 12th May 1981)* |
| **117** | Partition Coefficient (n-octanol/water), HPLC Method *(updated Guideline, adopted 1st February 2004)* |

# Section 2 – OECD Effects on Biotic Systems

**ADOPTED TEST GUIDELINES**

| TG No. | Title |
|---|---|
| **201** | Alga, Growth Inhibition Test *(Updated Guideline, adopted 7 June 1984)* |
| **202** | *Daphnia* sp. Acute Immobilisation Test and Reproduction Test *(updated Guideline, adopted 1st February 2004)* |
| **203** | Fish, Acute Toxicity Test *(Updated Guideline, adopted 17th July 1992)* |
| **208** | Terrestrial Plants, Growth Test *(Original Guideline, adopted 4th April 1984)* |
| **210** | Fish, Early-Life Stage Toxicity Test *(Original Guideline, adopted 17th July 1992)* |
| **211** | *Daphnia magna* Reproduction Test *(Original Guideline, adopted 21st September 1998)* |
| **216** | Soil Microorganisms, Nitrogen Transformation Test *(Original Guideline, adopted 21st January 2000)* |
| **218** | Sediment Water Chironomid Toxicity Test Using Spiked Sediment *(Original Guideline, adopted 1st February 2004)* |
| **219** | Sediment Water Chironomid Toxicity Test Using Spiked Water *(Original Guideline, adopted 1st February 2004)* |
| **220** | Enchytraeidae Reproduction Test *(Original Guideline, adopted 1st February 2004)* |
| **222** | Earthworm Reproduction Test (*Eisenia fetida/Eisenia Andrei) (Original Guideline, adopted 1st February 2004)* |

# Section 3 – OECD Degradation and Accumulation

**ADOPTED TEST GUIDELINES**

| TG No. | Title |
|---|---|
| **305** | Bioconcentration: Flow-through Fish Test *(Updated Guideline, adopted 14th June 1996)* |
| **307** | Aerobic and Anaerobic Transformation in Soil (*Original Guideline, adopted 24 April 2002*) |
| **308** | Aerobic and Anaerobic Transformation in Aquatic Sediment Systems (*Original Guideline, adopted 24 April 2002*) |

# Section 4 – ISO Guidelines

## ADOPTED TEST GUIDELINES

| ISO No. | Title |
|---|---|
| 10253 | Marine algae growth inhibition test with *Skeletonema costatum* and *Phaeodactylum tricornutum* |
| 14669 | Determination of acute lethal toxicity to marine copepods (Copepoda, Crustacea) |