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Guidance for Industry

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

VICH GL38

This guidance document is being distributed for comment purposes only

This draft 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 requiring 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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ENVIRONMENTAL IMPACT ASSESSMENT (EIA'S) FOR VETERINARY MEDICINAL PRODUCTS (VMP'S) – PHASE II DRAFT GUIDANCE

Recommended for Adoption

at Step 3 of the VICH Process

in October 2003 by the VICH SC for release for consultation at Step 4.

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 will be recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

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

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on safety of residues of veterinary drugs in the environment. 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 statute(s) and/or regulation(s). 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 (VMP's) identified as requiring data during the Phase I process. It also aims to be a major contribution towards the common use of test methods used to generate these data.

It needs to be kept in mind that guidance should not consist of rigid stipulations, but should make clear recommendations on the minimum criteria 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 Environmental Impact Assessment (EIA) requirements, 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 are 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 VMP's. Such expertise is important in evaluating the relevance of available data, for predicting environmental exposures, for identifying needed 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 these guidances 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 VMP's, 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 VMP's among 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 EIA's 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 developed for a given VMP.

2.1 Protection Goals

Legislation and policy on environmental quality in the VICH regions set out the protection goals for water, soil, sediment, groundwater, drinking water, air, species and habitats, and these should therefore be 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 VMP's to affect non-target species in the environment, including both aquatic and terrestrial species. It is not possible to evaluate the effects of VMP's on every species in the environment that may be exposed to the VMP following its administration to the target species. The species 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 VMP's 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 required, 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 tests for physical/chemical properties, environmental fate and environmental effects for both Tier A and Tier B, as well as a description of how to determine when tests at the latter level 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, it is recommended that then the applicant/sponsor progress to Tier B to refine the EIA. VMP's with greater potential to impact the environment may be expected to move to Tier B, the nature of the testing dependent on the findings at Tier A, refinement of the relevant PECs, and taking into account any other relevant information.

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

For certain VMP's, 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 VMP's 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 topicals or those added directly to water, most VMP's first pass through the animal to which it is administered. Generally the most significant environmental exposure results from excretion either of unchanged active ingredient (AI) 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 incorporates information on predicted environmental concentration (PEC) and the predicted no effect concentrations (PNEC) on non-target organisms. The PEC makes use of available data on excretion of the AI and relevant metabolites from the target species and data on the environmental fate. The RQ should be compared against a value of 1, and a value less than one generally indicates that no further testing is recommended. However, in some circumstances, professional judgement is important for a final determination.

The PEC of the RQ is defined as the concentration of the AI and metabolites predicted to be present in the environment. 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 recommendations to determine PECs. The applicant/sponsor should determine the most appropriate method of estimating exposures for the region of interest for a particular VMP based on regulatory guidance.

2.5 Assessment Factors

An assessment factor (AF) is a numerical factor that is applied to the endpoint value of an effects study to derive a PNEC. These factors are intended to cover uncertainties created by intra- and inter-laboratory and species variation, the extrapolation from laboratory test 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 recommended to be used in the assessment. A factor of 1000 is designed to be conservative and protective and is recommended 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.

2.6 Test Guidelines

The specific test guidelines/protocols recommended in Phase II are OECD/ISO studies in finalized form. This has the advantage of ensuring that environmental tests are current and broadly acceptable to regulatory authorities on a worldwide basis. Lack of a specific study recommendation, however, does not eliminate the need 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 and as such regulatory flexibility is needed. It is preferred that studies 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 in accordance with GLP, they may not be accepted in some VICH regions.

2.7 Metabolites

In triggering a Phase II assessment, the PEC is based on the total residue approach, as described in the Phase I document. The fate of chemicals in the environment is dependent on their chemical and physical properties. These properties will vary between the AI and the individual excreted metabolites, for example, the latter may be more water-soluble than the parent and may be more mobile and/or more persistent in the soil environment. This issue should be considered as part of the Phase II assessment.

In general, the data generated at Phase II will be on the AI, but the risk assessment should also consider relevant metabolites. Information on the identity of these should be available from excretion studies.

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 drug.

If the RQ is ≥1 for one or more tested species, then metabolism/excretion data from the residues part of the dossier should be considered as part of the PEC refinement. Metabolites representing 10% or more of the administered dose and which do not form part of biochemical pathways should be added to the active ingredient 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.

2.8 Special Consideration of Biodegradation Data

At Tier A, if the RQ is <1 for all the non-target species tested, it is recommended that the assessment should stop. However, there may be special cases with very persistent VMP's where, based on the soil/aquatic biodegradation tests, the $PEC_{initial}$ should be recalculated due to the possibility of accumulation in the environment.

Further, degradation products formed during environmental fate studies may be subject to investigation with respect to their persistence and mobility. It should be noted that an individual substance may be both an excreted metabolite and a degradation product in the environment.

In both cases guidance should be sought from the regulatory authority.

3 RECOMMENDED TESTS AT TIER A AND TIER B

Exposure to both the terrestrial and aquatic compartment may be recommended for a particular VMP depending on its route of environmental introduction. For instance, VMP's 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, VMP's used to treat pasture animals may impact aquatic as well as terrestrial non-target species. Therefore there should be a common set of criteria/tests and methods that will be used when testing is recommended. These tests and methods can be used for all three branches or just two, e.g. intensive terrestrial/pastures 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 tests for that compartment. However, sound scientific evidence should be presented in the dossier in support of the omission of these tests.

This section summarizes the tests 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 tests recommended at this level.

All testing should be carried out on the AI, with the possible exception of VMP's such as pro-drugs that are quickly and efficiently metabolized into a single product where it may be more appropriate to test the metabolite.

3.1 Tier A Testing

3.1.1 Tier A Physical-Chemical Properties Studies

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

Table 1 – Physical-chemical Tests at Tier A

Test	Guideline recommended
Water Solubility	OECD 105
Dissociation Constant	OECD 112
UV-Visible Adsorption Spectrum	OECD 101
Melting Temperature	OECD 102
Vapour Pressure*	OECD 104
n-Octanol/Water Partition Coefficient**	OECD 107 or 117

* Calculation only, though a test is recommended when other physical-chemical properties, e.g. molecular weight, melting temperature, thermogravimetric analysis suggest that the vapor pressure may exceed 10^{-5} Pa at 20°C.
** This criterion is not directly applicable to ionizable substances at environmental pH. The $\log K_{ow}$ for such substances should be measured on the non-ionized form at a relevant pH (i.e., below the pK for a free acid, or above the pK for a free base).

3.1.2 Tier A Environmental Fate Studies

Table 2 gives the recommended tests 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 tests 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

Test	Guideline recommended
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/sediments.
** These tests are recommended only for the terrestrial and aquaculture branches, respectively. It may be appropriate to do the latter test under salt water 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 tests and AFs recommended in Tier A for both direct and indirect aquatic exposures. Testing of 3 taxonomic levels is recommended in the harmonized guidance. At least one fish, one aquatic invertebrate and one algal species should be tested and the PNEC estimates for all species used individually for the RQ calculations.

VMP's to be used in fresh water should be studied using fresh water species and under freshwater conditions. Those used in sea water should be studied using seawater species and under sea water conditions. Only the fresh water tests should be conducted for VMP's used only on terrestrial animals. Species used should be characteristic of the environmental conditions (temperature range especially) in the region of use.

Table 3 – Tier A aquatic effects studies

Medium	**Tests**	**Toxicity endpoint**	**AF**	**Recommended Guidelines**
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
Seawater	Algal growth inhibition	EC_{50}	100	ISO 10253
Seawater	Crustacean acute toxicity	EC_{50}	1000	ISO 14669
Seawater	Fish acute toxicity	LC_{50}	1000	Seek regulatory guidance

* For antibiotics, 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 tests and AFs recommended in Tier A for soil exposures. These are generally only applicable to VMP's used for terrestrial treatments. All tests should be done and the PNEC estimates for all species used individually for the RQ calculations. For endo/ectoparasiticides used in intensive animal industries only, some regulatory authorities may seek additional information on the toxicity to non-target insects.

Table 4 - Terrestrial effects studies at Tier A

Tests	Toxicity endpoint	AF	Recommended Guidelines
Nitrogen Transformation (28 days)*	<± 25% of control	**	OECD 216
Terrestrial plants	EC_{50}	100	OECD 208
Earthworm Subacute/reproduction	NOEC	10	Draft OECD 222

* Test should be conducted at 1X and 10X the maximum estimated 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 predicted concentration) and control is equal or less than 25% at any sampling time before day 28, the VMP may be evaluated as having no long term influence on nitrogen transformation in soils. If this is not the case, the test should be extended to 100 days at Tier B (see Table 9).

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

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

Tests	Toxicity endpoint	AF	Recommended Guidelines
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 tests, but the WG notes the ongoing work in developing standardized tests for dung fly and dung beetle larvae and their inclusion into the OECD Test Guidelines Program.

Tests for toxicity to vertebrates (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 this case the applicant should consider the mammalian and (if available) avian toxicity data and seek regulatory guidance as to whether additional data are recommended. Similarly if the $\log K_{ow} \geq 4$, the risk of accumulation and further biomagnification through the food chain should be considered (again regulatory guidance should be sought).

3.1.4 PEC Refinement at Tier A

The risk assessment approach that is recommended is to compare the worst case $PEC_{initial}$ derived by the methods described in Sections 4-6 with the PNEC derived for each of the tested organisms as described above. In many cases, the risk assessment based on the worst case RQ should be

sufficient to conclude that an acceptable environmental risk is posed by VMP's that have entered Phase II (i.e., the RQ for all species is <1). However, there will be cases where an unacceptable risk is indicated for one or more organisms (RQ ≥1) and further refinement to the assessment is recommended.

The first step should be to refine the worst case $PEC_{initial}$ at Tier A through consideration of the metabolism/excretion information and the biodegradation in manure/soil/aquatic systems data. The $PEC_{refined}$ should then be compared with the PNEC for the affected species and a new RQ determined for each. If the RQ is now <1 for all species, the assessment should stop.

If the RQ is still ≥1 for any of the species tested, then the chemical should move to Tier B and testing for the affected species is recommended.

For pasture treatments if the RQ is ≥1 for dung insects from the worst case $PEC_{dung\text{-}initial}$, 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 VMP 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 recommended criteria for testing at Tier B are listed below in Table 6. While the main recommended criteria for advancing to Tier B is when the RQ is ≥1 after PEC refinement, there are also two cases relating to bioaccumulation and sediment toxicity where Tier B testing may be relevant.

Table 6 Recommended Criteria to go to Tier B testing

Recommended Triggers	**Further recommended testing**
RQ ≥1*	Effects tests for affected species only at Tier B
$logK_{ow}$ ≥4**	Bioconcentration test in fish at Tier B
If RQ for aquatic invertebrate ≥1*, consider $PEC_{sediment}/PNEC_{aquatic\ invertebrate}$. If ≥1, test is recommended. ***	Effects test in sediment species at Tier B

* Based on the $PEC_{refined}$

** This criterion is not directly applicable to ionizable substances at environmental pH. The $logK_{ow}$ for such substances should be measured on the non-ionized form at a relevant pH (i.e., below the pK for a free acid, or above the pK for a free base).

*** 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 test, preferably long-term, with benthic organisms using spiked sediment should be conducted to allow a realistic risk assessment appropriate to the sediment compartment to be carried out.

3.3 Tier B Testing

3.3.1 Tier B Physical-Chemical Properties Studies

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

3.3.2 Tier B Environmental Fate Studies

If the $\log K_{ow}$ is ≥4, evidence from metabolism/residues/excretion and biodegradation studies, together with toxicity, bioavailability and/or aquatic exposure, should be considered to see whether there is the potential for bioaccumulation to occur. If so, the test listed in Table 7 is recommended to be carried out at Tier B. If in doubt, regulatory guidance should be sought.

Table 7 Environmental fate studies at Tier B

Recommended Test	Recommended guideline
Bioconcentration in fish	OECD 305

If the Bioconcentration Factor (BCF) is ≥1000, further regulatory guidance should be sought.

3.3.3 Tier B Environmental Effects Studies

3.3.3.1 Tier B Aquatic tests

The tests in Table 8 are recommended only for those cases where the RQ for the affected species is ≥1 following use of the $PEC_{refined}$ (see section 3.1.4).

Table 8 Aquatic effects studies at Tier B

Environment	Recommended Tests	Endpoint	AF to derive PNEC	Recommended guidelines
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***
Seawater	Algae growth inhibition*	NOEC	10	ISO 10253
Seawater	Crustacean chronic toxicity or reproduction	NOEC	10	Seek regulatory guidance
Seawater	Fish chronic toxicity	NOEC	10	Seek regulatory guidance
Seawater	Sediment invertebrate species toxicity	NOEC	10	Seek regulatory guidance

* Using the same test and species as in Tier A but the NOEC is used in Tier B.
** Alternative tests for Fish, short term toxicity test on embryo and sac-fry stage (OECD TG 212) and Fish juvenile

growth test (OECD TG 215) are not favored, 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.
*** Draft guidelines at this stage. 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 ≥1, further regulatory guidance should be sought.

3.3.3.2 Tier B Terrestrial effects studies

The tests in Table 9 are recommended only for those cases where the RQ for the affected species is ≥1 following use of the $PEC_{refined}$ (see above).

Table 9 - Terrestrial effects studies at Tier B

Recommended Tests	Recommended method	Test endpoint	AF to derive long-term PNEC
Nitrogen Transformation (100 days – extension of Tier A test)	OECD 216	<± 25% of control	*
Terrestrial plants growth, more species**	OECD 208	NOEC	10
Earthworm	None recommended	-	-

* 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 predicted concentration) and control is equal or less than 25% at any sampling time before day 100, the VMP should be evaluated as having no long term influence on nitrogen transformation in soils.
** The test should be repeated on two additional species from the most sensitive species category in the Tier A test, in addition to repeating the test on the most sensitive species.

If after the Tier B testing the RQ is >1, further regulatory guidance should be sought.

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

Table 10 – Additional Tier B considerations for pasture treatments

Recommended Trigger for Tier B	Recommended Tier B, Effects studies
Dung insects	None recommended

4 AQUACULTURE BRANCH

4.1 Introduction

This section of the Phase II guidance deals with the environmental risk assessments for VMP's used in aquaculture. A variety of VMP's 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 those 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 a recommended 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 VMP may initially be distributed evenly within an area of water around the facility. Eventually more widespread distribution in the environment of the VMP 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 VMP to be removed by adsorption/degradation, prior to discharge to surface waters.

A recommended decision tree/flow diagram is presented in Figure 1 at the end of this section as an overview of the recommended risk assessment process for various types of VMP's 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

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

4.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the tests 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 VMP to photolyse or hydrolyse, then photolysis or hydrolysis tests may be conducted.

4.2.1.3 Environmental effects studies

Table 3, Section 3.1.3.1 gives the tests and AFs recommended in Tier A. At least one species should be tested 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 species.

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 worst case $PEC_{sw\text{-}initial}$.

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 VMP 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, will depend on how much VMP is diluted 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 species determined during aquatic toxicity testing should be compared with the $PEC_{sw\text{-}initial}$. If the RQ is <1 for all species, no further assessment is recommended. However, if the RQ is ≥1, the worst case $PEC_{sw\text{-}initial}$ should be refined, using a number of mitigations as described in Section 4.2.2.3, and the RQ recalculated.

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

The $PEC_{sw\text{-}initial}$ calculations are based on worst-case assumptions that assume that all of the drug 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. These factors 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 $PEC_{sediment}$ (PEC_{sed})

4.2.3.1 Calculation of PEC_{sed}

If the RQ for the aquatic invertebrate test is still ≥1 following the calculation of $PEC_{sw\text{-}refined}$, the PEC_{sed} should be calculated to compare with the $PNEC_{aquatic\ invertbrate}$ to indicate whether a toxicity

test for sediment species 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 $PEC_{sed\text{-}initial}$, 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. The calculation is worst case and if on conversion of the $PNEC_{sed}$ to $PNEC_{water}$ and comparison the RQ is $\geq$1, the $PEC_{sed\text{-}initial}$ should be further refined, based on concentrations in the sediment as determined by the concentrations in water and the sediment-water partition coefficient.

4.2.3.2 Calculation of PEC_{sed} in cases of VMP's added to feed

It is often convenient to administer VMP's in with 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 settle to the sediment under the net pens and for a distance beyond the net pens. For such VMP's it is also recommended 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 feces (in absence of data to the contrary assume this is 100% - % uneaten feed);
- Area of sediment directly beneath the net pen(s) and distance beyond net pen(s) in which uneaten feed and feces are deposited, m^2;
- Depth to which the VMP is distributed in sediment, cm;
- Density of sediment, g/cm^3.

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

Once the PEC_{sed} has been calculated it should be compared with the $PNEC_{aquatic\ invertbrate}$ as described in Section 4.2.3.1 to indicate whether a toxicity test for sediment species should be conducted at Tier B.

4.3 Tier B

4.3.1 Triggers for further testing in Tier B

As noted above, the main criteria recommended for consideration of further testing at Tier B for VMP's used in aquaculture is if the RQ based on the $PEC_{sw\text{-}refined}$ is ≥1 for one or more of the tested species.

4.3.2 Data recommended in Tier B

4.3.2.1 Physical-chemical properties

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 consideration of the excretion and degradation test results, the bioconcentration test in fish listed in Table 7 is recommended for VMP's used in aquaculture at Tier B.

4.3.2.3 Environmental effects studies

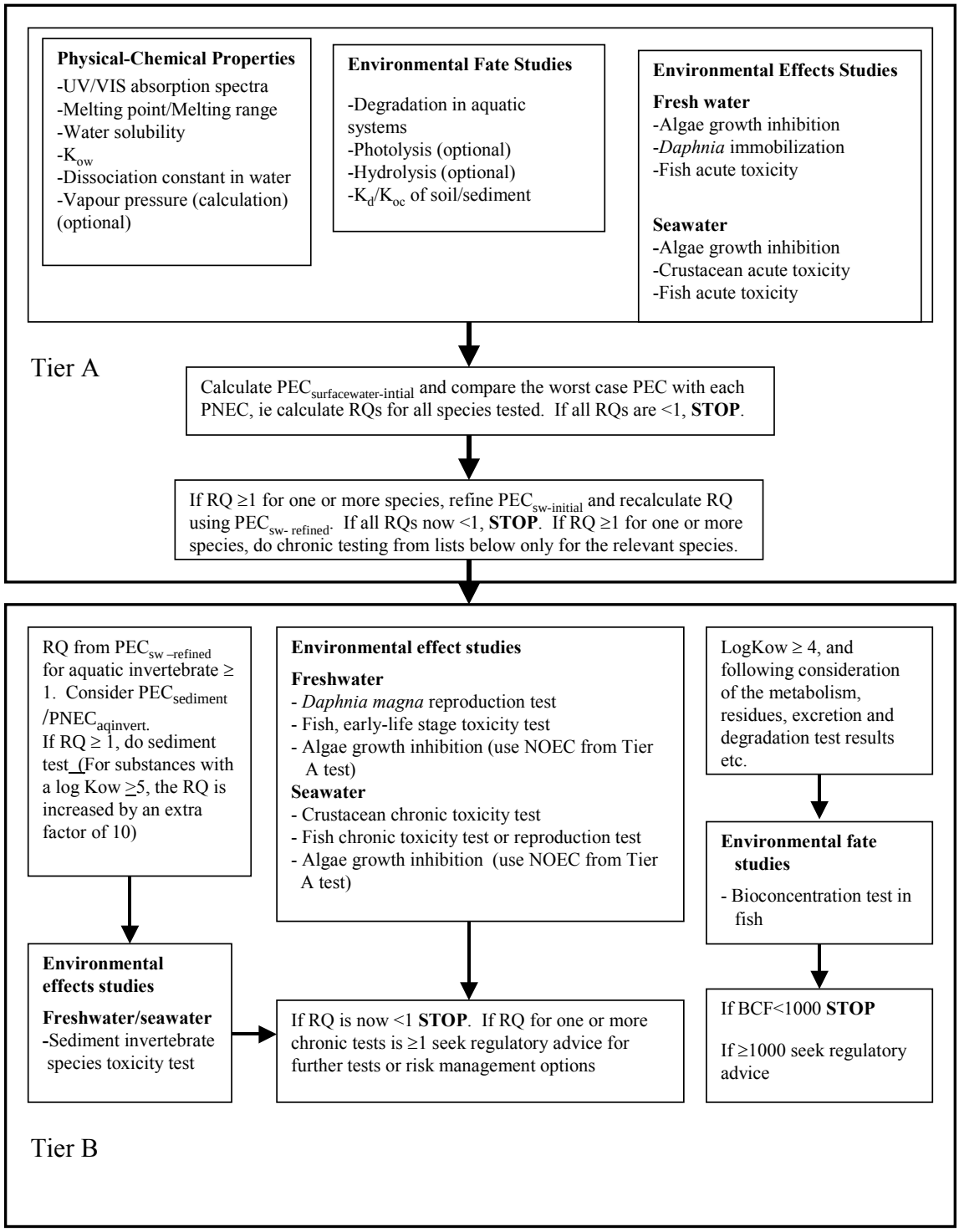
If the RQ is still ≥1 for one or more aquatic species when the $PEC_{sw\text{-}refined}$ is compared with the PNECs calculated for the acute tests conducted in Tier A, chronic testing for that particular species is recommended as indicated in Table 8 of Section 3.3.3.1.

If following refinement the RQ for an aquatic invertebrate in surface water is ≥1, the $PEC_{sed\text{-}refined}/PNEC_{aquatic\ invertebrate}$ should be considered. If RQ is ≥1, a sediment invertebrate toxicity test 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, i.e., for VMP's which still have an RQ≥1, then the applicant should 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 VMP's used in intensive terrestrial animal production.

Intensive terrestrial animal operations 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 recommended decision tree/flow diagram is presented in Figure 2 at the end of this section as an overview of the recommended risk assessment process for various types of VMP's used in intensive terrestrial animal operation. 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 intensive terrestrial animal production 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

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

5.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the tests recommended in Tier A. For VMP's used in the intensive terrestrial animal industry the biodegradation test should be conducted only in soil. If initial chemical studies indicate a potential for the VMP to photolyse or hydrolyse, then photolysis or hydrolysis tests may be conducted.

5.2.1.3 Environmental effects studies

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

Table 4, Section 3.1.3.2 gives the terrestrial toxicity tests and AFs recommended in Tier A. The recommended tests 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 species should 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 VMP's in the intensive terrestrial animal industry 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 active ingredient 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;
- 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 $PEC_{soil\text{-}initial}$ calculations

In Phase II Tier A the $PEC_{soil\text{-}initial}$ should first be calculated and used in the risk assessment. As noted in Section 2.7 this will assume 100% excretion of the administered dose as parent VMP and should 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 VMP to the same area of land. As noted in Section 2.8, 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 species determined during terrestrial toxicity testing should be compared with the $PEC_{soil\text{-}initial}$. If the RQ is <1 for all species tested, no further assessment is recommended. However, if the RQ is ≥1 for one or more species, the worst case $PEC_{soil\text{-}initial}$ should be refined, as described in Section 5.2.2.3, and the RQ should be recalculated.

5.2.2.3 Refinement of PEC_{soil}

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 2.7, where excretion data are available then the active ingredient 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 AI and relevant metabolites during storage of manure before spreading on fields, as appropriate; and
- by degradation of AI and relevant metabolites in the field, using the results of the laboratory soil degradation study from Tier A. Time to mineralization 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, VMP's 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 recommended to calculate PECs for both surface and groundwater.

5.2.3.1 $PEC_{sw\text{-}initial}$ calculations at Tier A

$PEC_{sw\text{-}initial}$ should be calculated from any form of indirect entry into surface water. $PEC_{sw\text{-}initial}$ should be 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 VMP, the amount of rainfall and the proportion that is likely to run off, and soil hydrology.

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

5.2.3.2 $PEC_{groundwater}$ (PEC_{gw}) calculations

The factors important in movement to groundwater include the physical and chemical properties of the VMP, the amount of soil organic matter, amount of rain, depth to the aquifer or seasonally saturated layer and the presence or absence of by-pass flow to a permeable substrate.

The PEC_{gw} 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 microbiota of groundwater.

5.3 Tier B

5.3.1 Triggers for further testing in Tier B

As noted above, the main recommended criteria for consideration of further testing at Tier B for VMP's used on intensively reared animals is if the RQ is ≥1 for one or more (both aquatic and terrestrial) of the tested species.

5.3.2 Data recommended in Tier B

5.3.2.1 Physical-chemical properties

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

5.3.2.2 Environmental fate studies

As noted in Section 3.3.2, if the $\log K_{ow}$ is ≥4, the bioconcentration test in fish listed in Table 7 is recommended at Tier B. However, it is expected that for intensively reared animals, based on

consideration of the excretion or biodegradation studies and the low aquatic exposure determined by the $PEC_{sw\text{-}refined}$, the test would rarely be recommended.

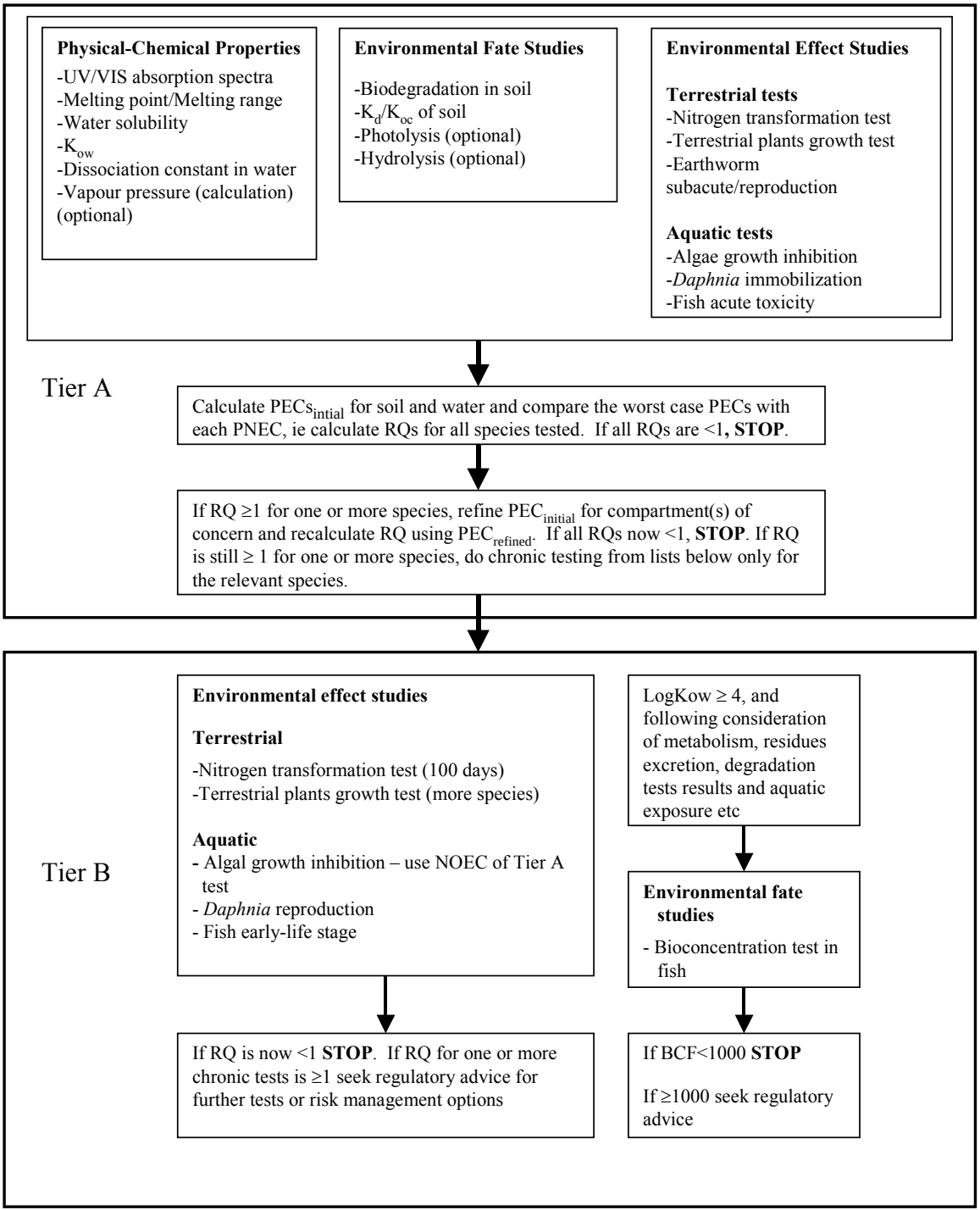
5.3.2.3 Environmental effects studies

If the PECs the RQ is still ≥1 for one or more species (both aquatic or terrestrial) when the $PEC_{soil/sw\text{-}refined}$ is compared with the results of the acute tests conducted in Tier A, chronic testing for that particular species should be carried out as indicated in Tables 8 and 9 of Section 3.3.3.

5.3.3 Further assessment

If there is still an indication of risk on completion of the Tier B assessment, i.e., for VMP's which still have an RQ≥1, or BCF ≥1000, then the applicant should discuss their dossier and proposals for

Figure 2 - Decision tree/Flow diagram for VMPs used for intensively-reared terrestrial animals



further data or risk mitigation with the regulatory authority.

6 PASTURE ANIMALS BRANCH

6.1 Introduction

This section of the Phase II guidance deals with the recommended environmental risk assessment approach for VMP's 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/ha 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- and ecto-parasiticides used in animals at pasture and both of these are described in this guidance.

A recommended decision tree/flow diagram is presented in Figure 3 at the end of this section as an overview of the recommended risk assessment process for various types of VMP's 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

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

6.2.1.2 Environmental fate studies

Table 2, Section 3.1.2 gives the tests recommended in this area in Tier A. For pasture animal VMP's the biodegradation test should be conducted only in soil. If initial chemical studies indicate a potential for the VMP to photolyse or hydrolyse, then photolysis or hydrolysis tests should be conducted.

6.2.1.3 Environmental effects studies

Table 3, Section 3.1.3.1 gives the aquatic effects tests and AFs recommended in Tier A. For VMP's administered to pasture animals at least one species should be tested from each of the three taxonomic levels ie fish, invertebrates and algae, and the PNEC estimated for each species should be used for the RQ calculations.

Table 4, Section 3.1.3.2 gives the terrestrial effects tests and AFs recommended in Tier A. The tests 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 species should be used for the RQ calculations.

In the specific case of endo/ectoparasiticides used on pasture animals, the tests listed in Table 5 (Section 3.1.3.2) are also recommended at Tier A. 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 recommended study guidelines to use to assess toxicity to dung insects.

6.2.2 Calculation and comparison of PEC_{soil}

VMP's may be used on animals that are kept at pasture, as well as those being housed or kept in feedlots. Consequently, any excretion of the VMP in urine or feces 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 $PEC_{soil\text{-}initial}$ calculations

At Tier A, an initial calculation of $PEC_{soil\text{-}initial}$ is recommended for all VMP's 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 VMP excreted in both feces 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 active ingredient 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 data on:

- Excretion of the VMP, expressed as 100% total residue (AI and relevant metabolites) excreted;
- An assumption regarding depth of soil to which residue is distributed; and
- Livestock stocking density.

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

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

6.2.2.3 Refinement of PEC_{soil}

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} should 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 $PEC_{dung\text{-}initial}$

Some VMP's are excreted predominantly in the dung rather than in urine. Where such VMP's 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 products excreted predominantly in dung, the $PEC_{dung\text{-}initial}$ should be estimated. This is the maximum concentration of the VMP in dung, and initially it should be assumed that there are no excretion data of the VMP 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 have been estimated. However, there should also be an estimation of the concentration in dung, as these products have the potential to affect dung insects.

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

At this stage, the PNECs derived for dung fly and dung beetles should be compared with the $PEC_{dung\text{-}initial}$. In some regions earthworms have an important dung distribution role, and therefore the PNEC for this species from the soil test should also be compared with the $PEC_{dung\text{-}initial}$. If the RQ is <1 for all species tested no further assessment is recommended. However, if the RQ is ≥ 1, the worst case $PEC_{dung\text{-}initial}$ should be refined, as described in Section 6.2.3.3, and the RQ recalculated.

6.2.3.3 Refinement of PEC_{dung}

In Tier B, the concentration in dung, PEC_{dung}, should not be 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 VMP 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 mean and maximum concentration in dung excreted at each time point should be compared to the PNEC for the dung insects (beetle/fly). An assessment should then be made of the time period after treatment during which dung toxic to dung insects is excreted.

6.2.4 Calculation and comparison of PEC_{sw}

6.2.4.1 Surface water: $PEC_{sw\text{-}initial}$

VMP's 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 recommended to calculate PECs for both surface and groundwater (see Section 5.2.3 of this guidance).

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 should 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 veterinary medicines 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 product 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 VMP 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 products 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 VMP 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. However, it is documented that such events may have impacts on several km of watercourse.

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 is recommended to prevent this impact. Where this practice is allowed, data should be submitted to the regulatory authority to enable an assessment of the risk to the environment, as part of the authorization process for these products. These situations should be addressed by the applicant with the appropriate regulatory authority on a case-by-case basis.

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 the harmonized guidance. 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 species 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 worst case $PEC_{sw\text{-}initial}$ should be refined, as described in Section 6.2.4.4, and the RQ should be recalculated.

6.2.4.4 Refinement of $PEC_{sw\text{-}initial}$

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 Risk Quotients are ≥1 for aquatic life. 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

As noted above, the main recommended criteria for consideration of further testing at Tier B for VMP's used on pasture animals is if the RQ is ≥1 for one or more species (both aquatic or terrestrial) tested.

6.3.2 Data recommended for Tier B

6.3.2.1 Physical-chemical properties

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

6.3.2.2 Environmental fate studies

As noted in Section 3.3.2, if the $\log K_{ow}$ is ≥4, the bioconcentration test in fish listed in Table 7 is recommended at Tier B. However, it is expected that for pasture animals, based on the excretion or biodegradation studies and low aquatic exposure as determined by the $PEC_{sw\text{-}refined}$, the test would rarely be recommended.

6.3.2.3 Environmental effects studies

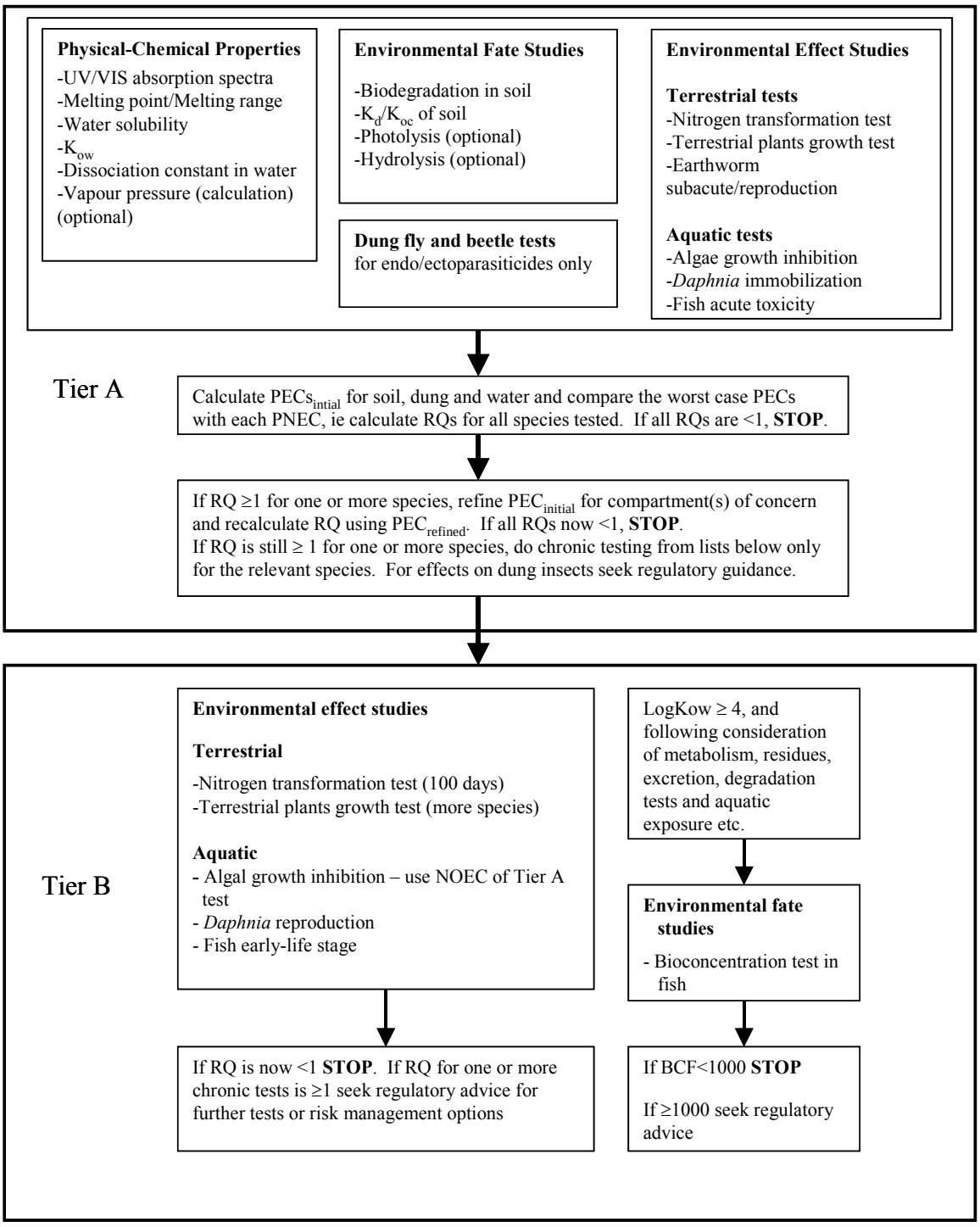
If following refinement of the PECs the RQ is still ≥1 for one or more species (both aquatic or standard terrestrial) when the $PEC_{soil/sw\text{-}refined}$ is compared with the results of the acute tests conducted in Tier A, chronic testing for that particular species should be carried out as indicated in Tables 8 and 9 of Section 3.3.3.

For the tests 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 species, then further testing should be conducted to determine the risk. Regulatory guidance should be sought on appropriate studies.

6.3.3 Further assessment

If there is still an indication of risk on completion of the Tier B assessment, i.e., for VMP's which still have an RQ≥1, then the applicant should 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)

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.
ISO	=	International Organization for Standardization
K_d	=	Sorption/desorption coefficient
K_{oc}	=	Sorption/desorption coefficient, normalized to organic carbon content
K_{ow}	=	n-Octanol/water partitioning coefficient
LC_{50}	=	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 authorization/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)".

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)*
103	Boiling point (*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 *(Original Guideline, adopted 30th March 1989)*

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 4 April 1984)*
203	Fish, Acute Toxicity Test *(Updated Guideline, adopted 17th July 1992)*
207	Earthworm, Acute Toxicity Tests *(Original Guideline, adopted 4th April 1984)*
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)*

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 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)
11268-2	Earthworms: Effects on reproduction