Phase Ⅱ　Tier A、Tier B　2 段階で実施

1. TierA

①$PNEC_{WATER}$（無影響濃度）と予測環境濃度（$PEC_{SURFACEWATER}$）の比較

以下の試験を行ない、$PNEC_{WATER}$（無影響濃度）を求める。

- 藻類の急性成長阻害試験　（OECD 201 準拠）
- ミジンコの急性遊泳阻害試験及び繁殖試験　（OECD 202 準拠）
- 魚類の急性毒性試験　（OECD 203 準拠）
- 藻類、ミジンコ、魚類を用いた長期試験

実施する試験の種類、数（組み合わせ）によって、以下のようなアセスメントファクターが与えられる。

得られるデータの種類	アセスメントファクター
藻類、ミジンコ、魚類の短期（急性）試験で得られる LC_{50} または EC_{50} のうち 1 つだけ	1000
ミジンコまたは魚類を用いた長期試験で得られる無影響濃度（NOEC）　（1 つだけ）	100
藻類、ミジンコ、魚類を用いた長期試験で得られる無影響濃度（NOEC）のうち 2 つ	50
藻類、ミジンコ、魚類を用いた長期試験で得られる無影響濃度（NOEC）（3 つすべて）	10

【判断】

これによって得られる無影響濃度（$PNEC_{WATER}$）を予測環境濃度（$PEC_{SURFACEWATER}$）と比較し、

$PEC_{SURFACEWATER}$ ＜ $PNEC_{WATER}$　→　終了（これ以上の試験の必要なし）

$PEC_{SURFACEWATER}$ ＞ $PNEC_{WATER}$　→　Tier B へ

注：以上は一般医薬品の場合であり、催眠性医薬の場合は、$PNEC_{AQUATIC}$ の試験を使用

②物理化学的特性を調べ、生物濃縮性、生物蓄積性を評価する。

- 活性汚泥呼吸阻害試験　（OECD 209 準拠）

【判断】

Kow（水/ｵｸﾀﾉｰﾙ分配係数）＞ 1000　→　TierB へ

Koc（吸着係数）＞ 10000 L/kg　→　TierB へ

2. TierB

必要に応じ、以下に示す試験を実施する。

- 魚類、ミジンコ及び藻類を用いた長期試験
- 微生物影響試験
- 魚類を用いた生物濃縮試験
- 生物分解性試験
- PEC（予測環境濃度）の再評価
- 陸地でのリスク評価
- 好気あるいは嫌気状態での土壌中の構造変化
- 土壌中の窒素移行試験
- 陸上植物の成長試験
- ミミズ急性毒性試験

これらの試験の結果から、環境リスクが予想される場合は、CPMP が科学的な助言を行なう。

CPMP 試験法リスト

Phase Ⅰ　試験無し

Phase Ⅱ　Tier A　物理化学及び運命試験

要求データ／試験	使用ガイドライン	EATH*
水溶解性	OECD 105	3.01
解離定数	OECD 112	3.04
UV 可視吸収スペクトル	OECD 101	3.05
融点	OECD 102	3.06
蒸気圧(任意)	OECD 104	3.03
オクタノール／水分配係数	OECD 107 もしくは 117	3.02
吸着 - 脱着	OECD 106	3.08
生分解(任意)	OECD 301	3.11,3.12
水中沈降系の有酸素、無酸素変化	OECD 308	
光分解(任意)	OECD モノグラフ No.61	3.10
pH 関数の加水分解	OECD 111	3.09

EATH: Environmental Assessment Technical Handbook

Phase Ⅱ　Tier A　水中／微生物影響試験

要求データ／試験	使用ガイドライン	EATH
藻類生長阻害試験	OECD 201	4.02
ミジンコ類急性遊泳阻害・繁殖試験	OECD 202	4.08
魚類急性毒性試験	OECD 203	4.11
活性汚泥呼吸阻害試験	OECD 209	

Phase Ⅱ　Tier B　陸生へのリスク評価

要求データ／試験	使用ガイドライン
土壌の有酸素及び無酸素変化	OECD 307
土壌微有機体：窒素変化試験	OECD 216
陸生植物生長試験	OECD 208
ミミズ急性毒性試験	OECD 207
Collembola　再生	ISO 11267

The European Agency for the Evaluation of Medicinal Products
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 July 2003
CPMP/SWP/4447/00 draft

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

DRAFT

NOTE FOR GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT OF MEDICINAL PRODUCTS FOR HUMAN USE

DISCUSSION IN THE SAFETY WORKING PARTY	June 1999 - November 2000
TRANSMISSION TO THE CPMP	January 2001
RELEASE FOR CONSULTATION	January 2001
DEADLINE FOR COMMENTS	July 2001
DISCUSSION IN THE SAFETY WORKING PARTY	October 2002 - June 2003
TRANSMISSION TO THE CPMP	June 2003
RE-RELEASE FOR CONSULTATION	July 2003
DEADLINE FOR COMMENTS	January 2004

Any comments to the Note for Guidance should be sent to the EMEA, SWP Secretariat (fax no +44 20 7418 8613) by end of January 2004.

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NOTE FOR GUIDANCE ON ENVIRONMENTAL RISK ASSESSMENT OF MEDICINAL PRODUCTS FOR HUMAN USE

1 INTRODUCTION

Council Directive 2001/83/EC states that an application for the marketing authorisation for a medicinal product for human use shall be accompanied by an environmental risk assessment. 2001/83/EC requires the applicant to indicate any potential risks exhibited by the medicinal product for the environment. It should be noted that 2001/83/EC relates to those risks to the environment arising from use, storage and disposal of the medicinal product and not to those arising from synthesis and manufacture of the product.

2 SCOPE OF THE GUIDANCE

This Note for Guidance is applicable for medicinal products for human use that apply to Council Directive 2001/83/EC, which are intended to be placed on the market in the European Union, renewals of such products and type II variations in the case of a major increase of the use of the product.

This Note for Guidance is not applicable for medicinal products containing or consisting of Genetically Modified Organisms; applicants are referred to the Note for Guidance on *Environmental Risk Assessment for Human Medicinal Products containing or consisting of GMOs* (CPMP/III/5507/94).

This Note for Guidance describes a two-phased environmental risk assessment of medicinal products when administered to patients.

3 GENERAL PRINCIPLES

Assessment of potential risks to the environment is a step-wise, phased procedure that may be terminated when sufficient information/data are available to either indicate that the medicinal product is unlikely to represent a risk to the environment or to identify and sufficiently characterise the potential risks. If relevant experimental data (e.g. metabolism) can be obtained from other parts of the dossier, these should be used in the assessment, and such studies therefore need not be repeated. Existing information on synergistic effects should be included in the risk assessment. If, based on the available information and data, the applicant concludes that the medicinal product is unlikely to represent a risk to the environment and that therefore it would not be necessary to generate additional experimental data, the applicant should justify this decision. When the medicinal product exhibits potential risks to the environment, the applicant should propose appropriate precautionary and safety measures to be observed when the product is administered to patients and/or for the disposal of waste products. These measures should be included in the Summary of Products Characteristics (SPC).

Emphasis should be given to the parent compound and/or metabolite(s), as determined by human excretion profile, however the assessment should consider any substance of concern. Although most excipients can be described as inert, it is nevertheless possible that some may warrant attention in relation to their potential for harmful environmental effects. This should be discussed in the Environmental Risk Assessment Report, where relevant.

The environmental risk assessment consists of two phases. The first phase (Phase I) assesses the exposure of the environment to the drug substance. Substances such as vitamins,

electrolytes, amino acids can be exempted from further testing because they are unlikely to result in significant exposure of the environment and will consequently be of low environmental risk. A justification should be provided within the expert report (see section 8). Certain substances e.g. endocrine disruptors may need to be addressed irrespective of the quantity released into to the environment.

In a second phase (Phase II), information about the physical/chemical, pharmacological and/or toxicological properties are obtained and assessed in relation to the extent of exposure of the environment. During the conduct of the tests required, the investigator shall consider whether further specific investigation on the fate and effects of the product on particular ecosystems is necessary. Phase II is divided in two parts, Tier A and B.

Table 1: The phased approach in the environmental risk assessment

Stage in regulatory evaluation	Stage in risk assessment	Objective	Method	Test / Data requirement
Phase I		estimation of exposure	action limits	no test requirement
Phase II tier A	screening	rapid prediction of risk	risk assessment	base set aquatic toxicology and fate
Phase II tier B	primary	standard approach to ensure consistent decision making	risk assessment	extended data set on emission, fate and effects
	secondary	substance and site-specific refinement		case-by-case; alternative approaches, TGD approach

Tier A begins an evaluation of the possible fate and effects of the drug substance and/or major metabolites.

If within Tier A, no risk is detected, there is no need to proceed to Tier B. If a risk is detected, then the fate and effects of the medicinal product in the relevant compartment should be adequately investigated in Tier B.

4 PHASE I ENVIRONMENTAL EXPOSURE ASSESSMENT

Of the different environmental compartments (aquatic, atmospheric, and/or terrestrial), those of major concern need to be considered.

It is generally assumed that for medicinal products emission patterns will mainly consist of a diffuse release into waste water systems due to excretion of the drug substance and/or its metabolites by patients. Residues of medicinal products may reach the terrestrial environment with landspreading of solid or semi-solid sewage sludge from water treatment facilities. (see Figure 1). Other patterns may occur in special situations, e.g., emission of inhalation anaesthetics or propellants into the atmosphere. The concentrations of drug substances and/or their metabolites in the air compartment are generally assumed to be low due to their low vapour pressure, low production volumes and significant dilution. However, specific

environmental concerns should be considered, for example, in the case of propellants for inhalation aerosols, where the potential risk for depletion of the ozone layer and/or 'greenhouse' should be assessed. Matters relating to the replacement of chlorofluorocarbons (CFC) are referred to in the Note for Guidance on *Replacement of Chlorofluorocarbons (CFC) in Metered Dose Inhalation Products* (CPMP/III/5378/93) and *Matters Relating to the Replacement of CFC's in Medicinal Products* (CPMP/III/5462/93). Where relevant, assessments of exposures and effects in the air compartment should be conducted on a case-by-case basis.

4.1 Environmental exposure assessment: initial considerations

The exposure assessment is based mainly on data on the release of the substance(s) under consideration into the environment and on certain physico-chemical properties of the substance(s). Other relevant information includes the use pattern of the product, the expected extent of use, the concentration of the substance(s) under consideration in urine and faeces, the degradation processes under typical environmental conditions and sewage handling and disposal practices.

Subsequent to the release into one environmental compartment and dispersion therein, a substance will be further distributed between the other compartments (water, air, soil, sediment and biota). This distribution process can be estimated using standard physico-chemical parameters of the medicinal product. The octanol/water partition coefficient is generally used as an indicator of bioconcentration. It may also be useful in the assessment of sorption to sediment and soil particles for the majority of narcotic substances. Polar substances or substances with reactive groups display a non-predictable behaviour and require testing. The vapour pressure and/or Henry's constant allow an assessment of the relative emission into the air compartment.

While distribution refers to the physical process of transfer from one phase or compartment to another (e.g. from water to sediment particles or to the atmosphere), elimination means the reduction in concentration of substances by chemical or biochemical processes. Thus, elimination of a substance may occur by hydrolysis, photolysis or biodegradation (or a combination thereof).

4.2 Environmental exposure assessment: the substance(s) to be evaluated

The substance(s) to be included in the environmental risk assessment should generally be determined based on the excretion profile in man. The main excretory moiety should generally be assessed. In most cases, however, it is sufficient to consider just the active entity (the parent compound, or the active metabolite for pro-drugs), especially when a $PEC_{SURFACEWATER}$ is calculated under worst case conditions (i.e., no removal, low water consumption per capita) in the relevant environmental compartment, and the PEC value obtained gives no reason for concern and for further environmental effect analysis.

4.3 Calculation of the Predicted Environmental Concentration (PEC)

The initial calculation of PEC in surface water assumes

- a percentage of the overall market penetration (market penetration factor: Fpen) within the range of existing medicinal products,
- the predicted amount used per year is evenly distributed over the year and throughout the geographic area,
- the sewage system is the main route of entry of the medicinal product into the surface water.

- there is no biodegradation or retention of the medicinal product in the sewage treatment plant (STP),
- metabolism in the patient is not taken into account.

The following formula should be used to estimate the PEC in the surface water:

$$PEC_{SURFACEWATER} = \frac{DOSEai * Fpen}{WASTEWinhab * DILUTION * 100}$$

Table 2: Default values for PECSURFACEWATER calculation in Phase I

Parameter	Symbol	Value	Unit	Origin 1)	Remarks
Input					
• Maximum daily dose of active ingredient consumed per inhabitant	DOSEai		[mg.inh^{-1}.d^{-1}]	A	The highest recommended dose should be used
• Percentage of market penetration	Fpen	1 (*)	[%]	D	Default
• Amount of wastewater per inhabitant per day	*WASTEWinhab*	200	[L.inh^{-1}.d^{-1}]	D	From TGD
• Dilution factor	*DILUTION*	10	[--]	D	From TGD
Output	$PEC_{SURFACEWATER}$		[µg/L]	O	
• Local surface water concentration					

(1) A = based on information from applicant, D = default, O = Output * see section 9.
NOTES

4.4 Action limits and conclusions

If the Phase I estimate of $PEC_{SURFACEWATER}$ value (predicted concentration of the substance in surface water) is below 0.01 µg/L, and no other environmental concerns are apparent, it may be assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

If this $PEC_{SURFACEWATER}$ value is above 0.01 µg/L a Phase II environmental effect analysis should be performed as described below (section 5).

These action limits may not be applicable when the integrated expert evaluation of pre-clinical safety together with the expert evaluation of ecotoxic potential suggests atypical ecotoxic effects based upon known effects from related substances or results of biological studies on the specific substance. The expert should make use of the information on pharmacodynamics, kinetics and on toxicology (including the mechanism of action) contained in the Marketing Authorisation Application (MAA) in determining whether a non-standard action limit is appropriate.

An integrated evaluation by an established Expert should be presented, and this should allow conclusions to be drawn on any unusual potential for adverse effects in eco-toxicology, such

10^{-8} 0.001 µ.
10^{-9} g/L = 1 ppb 10 ppb

as endocrine disruptor activity. Such adverse toxic effects may affect the environment at concentrations lower than 0.01 µg/L and therefore indicate lower PEC action limits.

In every case, the Applicant should justify the action limits applied and all action taken.

5. PHASE II: ENVIRONMENTAL FATE AND EFFECTS ANALYSIS

In Phase II, it is important to make use of all available documentation relevant to the environmental risk assessment of the product. This includes physico-chemical data, relevant pharmacological-toxicological and toxicokinetic studies and information on degradability, persistence or the potential for bioaccumulation of the active ingredient and relevant metabolites.

Phase II of the guidance document is based on a tiered approach to the environmental risk assessment comprising two tiers (Tier A and Tier B) for which there are data requirements for physical/chemical properties, environmental fate and environmental effects testing. The first tier, Tier A uses studies to allow for an initial assessment of risk based on exposure in the environmental compartment of concern. In Tier A the $PEC_{SURFACEWATER}$ is refined with information on the estimated market success of the medicinal product. This information is provided by the Applicant. The refined $PEC_{SURFACEWATER}$ is used in the risk quotient approach.

If the environmental risk assessment cannot be completed with such data due to a prediction of an unacceptable risk, then the investigator progresses to Tier B to obtain further data in order to refine the PEC as well as the PNEC.

Experimental studies should be performed according to Good Laboratory Practices (GLP). The guidelines and test protocols issued by the European Commission, OECD and ISO are to be followed whenever possible. Only valid and plausible test results should be used in the environmental risk assessment.

5.1 Phase II – Tier A initial environmental fate and effects analysis

In Phase II Tier A the base-set of data is generated assessing the fate and the effects of the medicinal product in the aquatic compartment and the sewage treatment plant (STP). The screening information provides for information on the toxicity of the medicinal product to environmental organisms, its degradability in the STP, its biodegradation in the aquatic environment, its sorption behaviour and its potential for bioaccumulation.

5.1.1 Tier A Physical-chemical properties and fate assessment

The Tier A screening data set provides for information on the fate of a medicinal substance in the environment. The data are used in three ways:

- To investigate whether a substance has intrinsic properties resulting in the potential for bioaccumulation and to identify so-called very persistent and very bioaccumulative (vPvB) and persistent, bioaccumulative and toxic (PBT) substances,
- to ascertain if terrestrial exposure with landspreading of sewage sludge is likely,
- to refine the $PEC_{SURFACEWATER}$.

Degradability is one of the important intrinsic properties of chemical substances that determine their potential environmental hazard. Non- or -poorly degradable substances will persist in the environment and may consequently have a potential for causing long-term adverse effects on biota. In contrast, degradable substances may be removed in sewage treatment plants or in the environment.

In surface water, the substance may be transformed through photolysis, hydrolysis, and biodegradation. The water sediment study gives information on the degradation of medicinal products in the aquatic environment. The degradation rates obtained may be used to refine the $PEC_{SURFACEWATER}$ in Tier B.

The sorption behaviour of substances in sewage sludge is described through the adsorption coefficient which is defined as the ratio between the concentration of the substance in the sewage sludge and the concentration of the substance in the aqueous phase at adsorption equilibrium. It is assumed that a substance with a high Koc value is retained in the STP and may reach the terrestrial compartment with landspreading of sewage sludge. If the average Koc value exceeds 10000 l/kg a Tier B risk assessment for fate and effects in the terrestrial compartment should be performed.

On an optional basis a test for ready biodegradability of the medicinal product in sewage treatment plant may be conducted. If the study demonstrates quick removal of the substance in the STP this information may be included in the environmental risk assessment. However, significant information on fate and effects of the medicinal substance in the STP is given with the results from the adsorption/desorption study, the water sediment study and the activated sludge respiration inhibition test.

The standard assay of ecotoxic effect studies usually provides information about the direct toxic effects of a substance. Chemicals showing bioaccumulation and biomagnification may pose an additional threat due to exposure of organisms higher in the food chain such as top predators and man. A basic assessment of the potential for bioaccumulation of a medicinal substance is given with the K_{OW}. If the n-octanol /water partition coefficient exceeds the value of 1000 further testing is indicated in Tier B in accordance with the EU Technical Guidance Document (TGD).

Table 3: PC-Data set and fate studies required in Phase II Tier A

Data requirement/test	Guideline to be used
Water Solubility	OECD 105
Dissociation Constant	OECD 112
UV-Visible Adsorption Spectrum	OECD 101
Melting Temperature	OECD 102
Vapour Pressure (optional)	OECD 104
n-Octanol/Water Partition (Kow)	OECD 107 or 117
Adsorption - Desorption Using a Batch Equilibrium Method	OECD 106
Ready biodegradability (optional)	OECD 301
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308
Photolysis (optional)	Seek regulatory guidance/ OECD Monograph No. 61
Hydrolysis as a Function of pH (optional)	OECD 111

5.1.2 Tier A aquatic effects studies

For the Tier A assessment approach, a standard acute toxicity test set on fish, daphnia and algae may be used to determine the $PNEC_{WATER}$. The lowest value of the respective LC_{50} or EC_{50} should be used for risk evaluation. The Applicant should justify the test species used.

The purpose of this analysis is to predict the concentration of the substance for which adverse effects are not expected to occur in the environmental compartment of concern, i.e. to estimate the predicted no-effect concentration (PNEC). Guidance on the assessment of adverse effects is given in the TGD.

Table 4 lists the tests required in Tier A. In accordance with the TGD only 3 trophic levels of testing are required. A minimum of one species should be tested from three trophic levels (fish, invertebrates and algae) and the lowest PNEC estimate should be used for the risk calculation (RQ). Blue-green algae (Cyanophyta) are recommended for effects testing of antimicrobials as they are more sensitive indicator organisms than green algae.

Table 4: Tier A aquatic effects studies

Tests	Recommended Guideline
Alga, Growth Inhibition Test	OECD 201
Daphnia sp. Acute Immobilisation Test and Reproduction Test	OECD 202
Fish, Acute Toxicity Test	OECD 203

Microbial communities may be affected by the active ingredients of medicinal products, particularly of those designed to inhibit the growth of pathogenic microbes. The microbial community most likely exposed to the highest concentrations of the medicinal product is the activated sludge community. In order to evaluate inhibiting effects of the medicinal product on these communities, the effects should be tested in those organisms or in representative species. The activated sludge respiration inhibition test (OECD 209) determines a $PNEC_{MICRO\text{-}ORGANISM}$ which is compared to the initial $PEC_{SURFACEWATER}$ (Table 5). If the risk quotient indicates a risk assessment for micro-organisms Tier B studies should be conducted. Detailed guidance on the effects assessment for micro-organisms in STP in addition to other suitable tests are provided in the TGD.

Table 5: Tier A microbial effects studies

Test	Recommended Guideline
Activated Sludge, Respiration Inhibition Test	OECD 209

5.1.3 Calculation of PNEC using assessment factors

The Predicted No Effects Concentration (PNEC) is calculated by applying an assessment factor to the values resulting from tests on environmental organisms from the compartment of concern, e.g. LC_{50}, EC_{50} or NOEC. The assessment factor is an expression of the degree of uncertainty in the extrapolation from the test data on a limited number of species to the 'real environment'. In general, more extensive data and longer duration of the tests reduce the degree of uncertainty and consequently the size of the assessment factor.

The assessment factor accounts for:

- extrapolation from acute to chronic toxicity
- inter-species variations of differences in sensitivity

- intra-species variability
- laboratory data to field impact extrapolation (additive, synergistic and antagonistic effects from the presence of other substances may also play a role here)

The assessment factors presented below (Table 6) are considered as general factors for narcotic substances. Recent laboratory findings indicate that higher assessment factors may be warranted for some drug substances. The applicant should justify the assessment factor used for PNEC determination. Specific comments on the use of assessment factors in relation to the available data as well as needs and justifications for changing the assessment factors are given in the Notes (2) and the TGD.

Table 6: Assessment factors to derive a PNECAQUATIC

Available data	Assessment factor
At least one short-term L(E)C50 from each of three trophic levels of the base-set (fish, Daphnia and algae)	1000
One long-term NOEC (either fish or Daphnia)	100
Two long-term NOECs from species representing two trophic levels (fish and/or Daphnia and/or algae)	50
Long-term NOECs from at least three species (normally fish, Daphnia and algae) representing three trophic levels	10

In cases where chronic tests have been performed, the assessment factor can be reduced as described in the TGD. The assessment factor may be reduced to 50 or 10 when more long-term data are available, particularly on sub-lethal endpoints addressing the concerns derived from the above mentioned information, or from tests in a number of species from different trophic levels.

5.1.4 PECGROUNDWATER risk assessment

An exposure assessment for groundwater is required. Two possible entries into the groundwater are considered, via bank filtration and via leaching through soil after slugde application to agricultural land. A simple estimation is $PEC_{INTERSTITIAL\ WATER} = PEC_{SURFACEWATER}$. The model EXPOSIT provides the estimation of the $PEC_{GROUNDWATER}$ from $PEC_{SURFACEWATER}$ based on a standardised scenario taking into account meteorological (rainfall) and application data. Elaborated leaching models for the calculation of groundwater exposure via leaching through soil are given by EU-FOCUS Group (e.g. PELMO and PEARL).

Since the Phase II Tier A risk assessment is based on a total residue approach and includes a $PEC_{SURFACEWATER}/PNEC_{AQUATIC}$ approach, no risk assessment for groundwater is needed. If a risk assessment in the terrestrial compartment is conducted due to high sorption characteristics of the medicinal product a $PEC_{GROUNDWATER}$ should be calculated.

5.1.5 Refinement of PECSURFACEWATER in Tier A

In Tier A the $PEC_{SURFACEWATER}$ is refined with an estimation for the market penetration of the medicinal product in an EU region or the EU. The penetration factor takes account of the sales forecast for the medicinal product. It should be based on health care statistics and/or epidemiological data supplied by the applicant.

The market penetration factor is calculated as follows.

$$F_{pen} = \frac{CONai*100}{DOSEai * inhabitants*365\ d/a}$$

Table 7: Calculation of Fpen

Parameter	Symbol	Unit	Remarks
<u>Input</u>			
• Estimated consumption of active ingredient in geographic region per year based on statistics and/or epidemiological studies	*CONai*	[mg.a^{-1}]	Normally: figures per country or regions
• Maximum daily dose of active ingredient consumed per inhabitant	DOSEai	[mg.inh^{-1}.d^{-1}]	
• Inhabitants in geographic area	inhabitants	[inh]	Normally: inhabitants of countries or regions
Output	*Fpen*	[%]	
• Percentage of market penetration			

5.2 Outcome of Tier A fate and effects analysis

At the end of Tier A information from the screening data set is available comprising short-term toxicity data for algae, Daphnia and fish, microbial inhibition and information on the biodegradability, the persistence, the log P_{OW} and the rate of adsorption (K_{OC}). The $PEC_{SURFACEWATER}$ has been refined with information on the sales forecast of the product.

- If the ratio $PEC_{SURFACE\ WATER}$: $PNEC_{WATER}$ for the medicinal product is below 1 and if no risk for bioaccumulation is assessed, further testing in the aquatic compartment will not be necessary and it can be concluded that the medicinal product is unlikely to represent a risk to the aquatic environment.
- If the ratio $PEC_{SURFACEWATER}$: $PNEC_{WATER}$ is above 1, further evaluation on the effects of the medicinal product in the aquatic environment are needed in Tier B.
- If the ratio $PEC_{SURFACE\ WATER}$: $PNEC_{MICRO\text{-}ORGANISM}$ is above 1, further evaluation of the effects of the medicinal products on micro-organisms are needed in Tier B.
- If the n-octanol/water partition coefficient indicates the transfer of the medicinal product from the aquatic environment into organisms and a potential to bioaccumulate (K_{OW} >1000), then the bioconcentration factor should be determined in Tier B.
- If the adsorption/desorption data indicates the affinity for a medicinal product to bind to sewage sludge in the STP (K_{OC} > 10000 l/kg) an environmental assessment of the medicinal substance in the terrestrial compartment should be conducted.

5.3 Tier B

If in Tier A a risk for the medicinal product in the environment has been assessed then a Tier B assessment should be conducted.

5.3.1 Tier B studies

In general, a risk that has been assessed in Tier A ($PEC_{SURFACEWATER}/PNEC_{AQUATIC}$) is followed by a Tier B long-term test programme on fish, Daphnia and algae. Assessment factors for long-term tests are lowered in accordance with section 5.1.3.

Deviations from the Tier B test programme are indicated if there is a variance of the effects among the trophic levels tested. An overview on suitable long-term test strategies is given in the decision table for aquatic toxicity testing in TGD.

If the results from the water sediment study (OECD 308) demonstrate extensive shifting of the drug substance to the sediment, testing of effects on sediment organisms might be indicated. A detailed strategy for further testing in order to refine the PNEC for the aquatic compartment can be found in the TGD.

5.3.2 Tier B Specific effects on the micro-organisms

If an inhibiting effect in the OECD Test 209 has occurred, further analysis of microbial toxicity should be conducted in Tier B. For the PNECMICRO-ORGANISMS a number of standardized tests on single micrbial species (e.g. *Pseudomonas putida*) are given in the TGD.

5.3.3 Tier B Bioaccumulation

Due to the potency of medicinal products special regard should be given to the potential of bioaccumulation. If the KOW indicates a potential for bioaccumulation, as a first step a bioconcentration test (OECD 305) should be conducted. Guidance on the assessment of bioaccumulation and biomagnification is given in the TGD.

If a substance is persistent and bioaccumulative, a vPvB assessment should be conducted. In case of persistent, bioaccumulative and toxic properties, a PBT assessment should be conducted. Criteria for identification and guidance on the assessment of PBT and vPvB substances are set out in the TGD.

5.3.4 Tier B Environmental fate analysis and PECSURFACEWATER refinement

The determination of the chemical composition of the total residue can refine the PEC. So far the risk approach has been based on the exposure to the total residue and the effect profile of the drug substance. Metabolism within the patient and transformation during environmental distribution may lower the amount of drug substance within the environmental compartment of concern. Chemical characterisation of the excreted residue is the first step. Characterisation of the transformation pathway within the environment (sewage, surface water, soil) may be performed subsequently. The potential risks of the metabolites should be assessed by, at least, an aquatic toxicity base set. There are no other data requirements on fate and effects for metabolites. Metabolites that are deemed to be of no concern are not assessed. The assessment should include those relevant human and environmental metabolite(s), which are deemed to be of concern and exceed 10 % of the total residue. Metabolites formed at levels <10% are not further considered. For human metabolites this percentage refers to the amount excreted. For transformation products formed in the environment this refers to the amount of drug substance applied in the respective test system (water/sediment, sewage, water, soil) used to characterise the transformation pathway. Formation of metabolites within animal or plant species in the environment is not considered. As a general rule, transformation of human metabolites in the environment need not be investigated, as they are expected to be part of the transformation pathway of the drug substance, that has been examined in Phase II Tier A. The refined risk assessment is performed using the refined PEC and the drug substance PNEC, as well as using the dedicated PEC and PNEC for the relevant (≥10%) metabolic fractions.

In Tier B the $PEC_{SURFACEWATER}$ may be refined with information from

- excretion, i.e. route(s) of excretion and qualitative and quantitative information on excreted compounds. This information is given in other parts of the MAA.
- adsorption of substances to sewage sludge in waste water treatment plants, using the data from the estimation of the adsorption coefficient (OECD 106),
- biodegradation of active ingredient and relevant metabolites in surface water, using the data from the water/sediment degradation study (OECD 308) and
- test for ready biodegradability in the STP (OECD 301). The ready biodegradability test is optional in Tier A but mandatory in Tier B assessment (Table 8).
- degradation with hydrolysis (OECD 102) and/or photolysis,

Table 8: Tier Environmental fate study

Test	Recommended Guideline
Ready biodegradability	OECD 301

The local surface water concentration should be refined as:

$$PEC_{SURFACEWATER} = \frac{Elocal_{water} * F_{stp}}{WASTEWinhab * CAPACITYstp * FACTOR * DILUTION}$$

$$\text{Where } Elocal_{water} = \frac{DOSEai * (F_{excreta}) * F_{pen} * CAPACITYstp}{100}$$

Table 9 summarises the parameters and default values used for the calculation of $PEC_{SURFACEWATER}$ in Phase II. In all cases, realistic worst case estimates should be used.

Table 9: Parameters and defaults for PECSURFACEWATER calculation in Phase II

Parameter	Symbol	Value	Unit	Origin [1]	Remarks
Input					
• Maximum daily dose of active ingredient consumed per inhabitant	DOSEai		[mg.inh^{-1}.d^{-1}]	A	The highest *recommended* dose should be used.
• Fraction of active ingredient excreted	*Fexcreta*		[--]	A	From toxicokinetic studies
• Amount of wastewater per inhabitant per day	*WASTEWinhab*	200	[L.inh^{-1}.d^{-1}]	D	From TGD
• Percentage of market penetration	*Fpen*		[%]	A	Value refined in Tier A
• Capacity of local sewage treatment plant (STP)	*CAPACITYstp*	10000	[inh^{-1}]	D	From TGD
• Fraction of emission directed to surface water	$Fstp_{water}$		[--]	C	Calculated by SimpleTreat[1]
• Dilution factor	*DILUTION FACTOR*	10	[--]	D	From TGD
• Factor taking the adsorption to suspended matter into account			[--]	C	From TGD[2]
Output	$Elocal_{water}$		[kg.d^{-1}]	O	
• Local emission to wastewater					
• Local surface water concentration	$PEClocal_{water}$		[ng/L]	O	

A = based on information from applicant; D = default, C = extra calculation, O = Output

Table 10 gives an overview on the different measures of $PEC_{SURFACEWATER}$ refinement in the tiered step-wise risk assessment:

Table 10: Refinement of the PECSURFACEWATER

Phase/Tier	F_{pen}	$Fstp_{water}$	$F_{excreta}$
Phase I	1	1	1 (no metabolism)
Phase II Tier A	refined by applicant	1	1 (no metabolism)
Phase II Tier B	refined by applicant	refined by SimpleTreat calculation and biodegradation test data	refined by toxicokinetic study

5.3.5 Tier B Terrestrial compartment: Environmental fate and effects testing

When indicated (KOC>10000 l/kg), the concentration of the medicinal product in the terrestrial compartment should be calculated. Risk assessment including PECSOIL calculation should be done by using methodologies as described in the European Technical Guidance Documents (TGD).

In general, a base set of tests investigating biodegradation in soil, toxicity to soil invertebrates and acute effects on terrestrial plants and micro-organisms should be conducted (Table 11).

Table 11: Tier B Terrestrial risk assessment studies

Data requirement/test	Guideline to be used
Aerobic and anaerobic transformation in soil	OECD 307
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216
Terrestrial Plants, Growth Test	OECD 208
Earthworm, Acute Toxicity Tests	OECD 207
Collembola reproduction	ISO 11267

6. PRECAUTIONARY AND SAFETY MEASURES TO BE TAKEN FOR ADMINISTRATION, DISPOSAL AND LABELLING

When the possibility of environmental risks cannot be excluded, precautionary and safety measures may consist of;

- Restricted clinical use, e.g. hospitals only
- Product labelling, Summary Product Characteristics (SPC), Package Leaflet (PL), etc. for patient use, product storage and disposal

Labelling should generally aim at minimising the quantity discharged into the environment by appropriate mitigation measures.

Appropriate disposal of unused pharmaceuticals, e.g. when shelf life is expired, is considered important to reduce the exposure of the environment. In order to enhance environmental protection, it is therefore recommended that – even for medicinal products that do not require special disposal measures - package leaflets (patient information leaflets) should include the following general statement:

" Medicines no longer required should not be disposed of via wastewater or the municipal drainage system. Return them to a pharmacy or ask your pharmacist how to dispose of them in accordance with the national regulations. These measures will help to protect the environment."

Additional labelling should be employed only when the assessment of the medicinal product points to an exceptional situation (e.g. radioactive isotope preparations or medicines concentrated in devices) in which circumstances the measures to be taken should be practical and realistic given the anticipated use of the product.

7. SCIENTIFIC ADVICE FROM THE CPMP

The applicant may request scientific advice from the CPMP -according to the EMEA procedures for such advice- on issues related to environmental risk assessment and on possible precautionary and safety measures to be taken with respect to the use and disposal of a medicinal product.

8. REPORTING – THE ENVIRONMENTAL RISK ASSESSMENT REPORT

The Expert Report should be based on the characteristics of the product, its potential environmental exposure, environmental fate and effects, and risk management strategies as appropriate. The conclusion of the report should be based on sound scientific reasoning supported by adequate studies and be presented in Module I of the dossier.

The Expert Report should include an evaluation the applicability of the environmental assessment performed. In particular, the report should provide:

1. An estimate of the potential environmental exposure (PEC) with an assessment of the underlying assumptions.
2. An assessment of possible risks to the environment from the point of view of use, and a presentation and evaluation of data in support of such risk evaluation,
3. An evaluation of precautionary and safety measures to be taken regarding the environmental release from use in patients, and disposal of unused products or waste materials derived from such products,
4. Proposals for labelling (SPC, PL etc.) which give an outline of the information that applicants could provide on precautionary and safety measures to be taken, for the purpose of reducing any risks to the environment, with regard to the administration to patients and disposal of waste products.

The Expert Report should state the justifications if any of the above evaluations are not found to be applicable for the medicinal product.

The curriculum vitae of the Expert should be provided.

9. NOTES

(1) Fpen

A 95 percentile of 0.954 % was calculated as the default penetration factor (Fpen). It is proposed to use a Fpen of 1% in the risk assessment.

The penetration factor (Fpen) represents the proportion of the population being treated daily with a specific drug substance. The default penetration factor was calculated as follows:

$$\text{Fpen [\%]} = \frac{\text{consumption [mg/year]} * 100}{\text{DDD [mg/d*inhab]} * \text{inhabitants [inhab]} * 365 \text{ d/year}}$$

The following data were used:

- Institut für Medizinische Statistik, Frankfurt/M., (IMS Health): IMS Health maintains a data bank "Chemical Country Profil" containing statistics for annual German consumption of about 2700 drug substances. This data base was considered representative for the drug consumption in the European Union.
- Defined daily dose values (DDD) values of the World Health Organisation (WHO). In total DDD-values for about 1450 drug substances were available.
- German population: 82 012 000 inhabitants

For the evaluation of the market penetration factor about 800 drug substances were taken into account. Those substances were established on the German market in 2001 and a DDD-value was available.

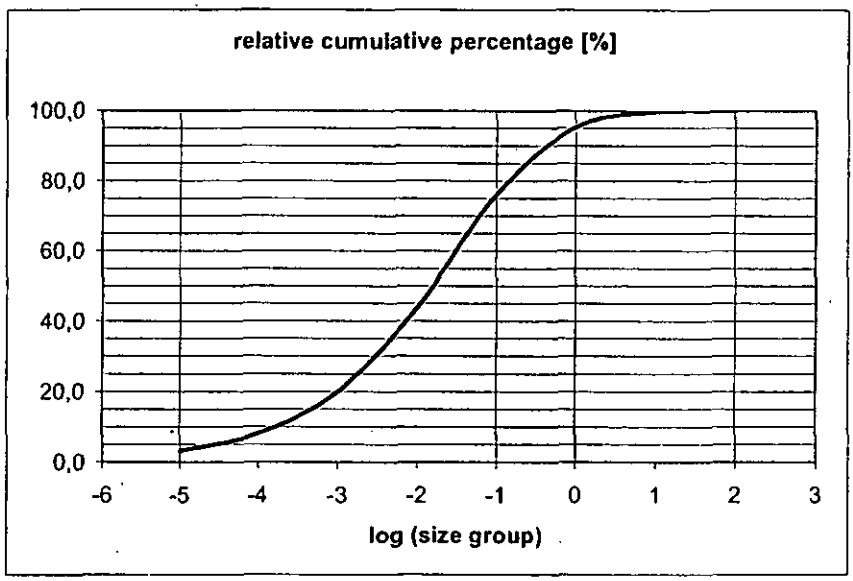

Figure 1: Cumulative frequency curve of the market penetration factor (Fpen)