COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)

DRAFT

GUIDELINE ON THE ENVIRONMENTAL RISK ASSESSMENT OF
MEDICINAL PRODUCTS FOR HUMAN USE

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<tr>
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Any comments to the Note for Guidance should be sent to the EMEA, SWP Secretariat (fax no +44 20 7418 8613) by end of April 2005.
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1 INTRODUCTION

An application for the marketing authorisation for a medicinal product for human use shall be accompanied by an environmental risk assessment. Directive 2001/83/EC, as amended requires the applicant to evaluate any potential risks of the medicinal product to the environment.

2 SCOPE OF THE GUIDELINE

This guideline is applicable to medicinal products for human use that fall under Directive 2001/83/EC, as amended. This guidelines applies in particular to new active substances. The Directive relates to those risks to the environment arising from use, storage and disposal of medicinal products. It should also be noted that this guideline is not applicable for the evaluation of environmental risks arising from the synthesis or manufacture of medicinal products. Applications for Orphan Medicinal Products need not be accompanied by an environmental risk assessment. Applications of 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).

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 in the environment 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 active substance and/or its 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 environmental risk. 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 active substance and/or its metabolite(s). Substances such as vitamins, electrolytes, amino acids, peptides and proteins can be exempted from testing because they are unlikely to result in significant exposure of the environment and will consequently be of low environmental risk. Certain substances e.g. endocrine disruptors may need to be addressed irrespective of the quantity released into the environment. In any case,
a justification should be provided within the Environmental Risk Assessment report in Module I of the Marketing Authorisation Application (MAA, see section 8).

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**

<table>
<thead>
<tr>
<th>Stage in regulatory evaluation</th>
<th>Stage in risk assessment</th>
<th>Objective</th>
<th>Method</th>
<th>Test / Data requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>pre-screening</td>
<td>estimation of exposure</td>
<td>action limit</td>
<td>no test requirement</td>
</tr>
<tr>
<td>Phase II Tier A</td>
<td>screening</td>
<td>initial prediction of risk</td>
<td>risk assessment</td>
<td>base set aquatic toxicology and fate</td>
</tr>
<tr>
<td>Phase II Tier B</td>
<td>primary</td>
<td>standard approach to ensure consistent decision making</td>
<td>risk assessment</td>
<td>extended data set on emission, fate and effects</td>
</tr>
<tr>
<td></td>
<td>secondary</td>
<td>substance and site-specific refinement</td>
<td>case-by-case; alternative approaches, TGD approach</td>
<td></td>
</tr>
</tbody>
</table>

Tier A begins with an evaluation of the possible fate and effects of the active substance and/or its 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 active substance and/or its metabolites in the relevant compartment should be adequately investigated in Tier B.

The exposure assessment is based mainly on data on the release of the active substance and/or its metabolites 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). 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).
3.1 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 it is sufficient to consider just the active substance and/or its metabolites (the parent compound, or the active metabolite for pro-drugs), especially when a $\text{PEC}_{\text{SURFACEWATER}}$ is calculated under worst case conditions (i.e., no removal, low water consumption per capita, no metabolism) in the relevant environmental compartment.

4 ENVIRONMENTAL EXPOSURE ASSESSMENT

All environmental compartments of major concern (aquatic, atmospheric, terrestrial) need to be considered. In most cases 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 2). 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 'global warming should be considered. 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 Phase I calculation of the Predicted Environmental Concentration (PEC)

In Phase I the PEC calculation is restricted to the aquatic compartment. The initial calculation of PEC in surfacewater assumes

- a percentage of the overall market penetration (market penetration factor: $F_{\text{pen}}$) 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 active substance and/or its metabolites into the surfacewater.
- there is no biodegradation or retention of the active substance and/or its metabolites in the sewage treatment plant (STP),
- metabolism in the patient is not taken into account. This approach will avoid metabolite testing in the early stages of the risk assessment.

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

\[
\text{PEC}_{\text{SURFACEWATER}} = \frac{\text{DOSE}_{\text{ai}} \times F_{\text{pen}}}{\text{WASTE}_{\text{Winhab}} \times \text{DILUTION} \times 100}
\]
Table 2: Default values for $\text{PEC}_{\text{SURFACEWATER}}$ calculation in Phase I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
<th>Origin</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Maximum daily dose of active substance consumed per inhabitant</td>
<td>DOSEai</td>
<td>[mg inh$^{-1}$ d$^{-1}$]</td>
<td>A</td>
<td>The highest recommended dose should be used</td>
<td></td>
</tr>
<tr>
<td>• Percentage of market penetration</td>
<td>Fpen</td>
<td>1(*)</td>
<td>[%]</td>
<td>D</td>
<td>Default</td>
</tr>
<tr>
<td>• Amount of wastewater per inhabitant per day</td>
<td>WASTEWinhab</td>
<td>200</td>
<td>[L inh$^{-1}$ d$^{-1}$]</td>
<td>D</td>
<td>From TGD</td>
</tr>
<tr>
<td>• Dilution factor</td>
<td>DILUTION</td>
<td>10</td>
<td>[-]</td>
<td>D</td>
<td>From TGD</td>
</tr>
<tr>
<td>Output</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Local surfacewater concentration</td>
<td>$\text{PEC}_{\text{SURFACEWATER}}$</td>
<td></td>
<td>[mg L$^{-1}$]</td>
<td>O</td>
<td></td>
</tr>
</tbody>
</table>

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

4.2 Action limits and conclusions

If the Phase I estimate of $\text{PEC}_{\text{SURFACEWATER}}$ value (predicted concentration of the substance in surfacewater) is below 0.01 µg/L$^1$, 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 $\text{PEC}_{\text{SURFACEWATER}}$ 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 preclinical 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 ecotoxicology, such 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 any 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.

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$^1$ The present action limit is based mainly on acute toxicity data and will therefore be revised when a sufficient amount of chronic data exists.
persistence or the potential for bioaccumulation of the active substance and/or 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\textsubscript{SURFACEWATER} is refined with information on the estimated market success of the medicinal product. This information is provided by the Applicant. The refined PEC\textsubscript{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 two 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,

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\textsubscript{SURFACEWATER} in Tier B.

The sorption behaviour of substances in sewage sludge is described through the adsorption coefficient (K\textsubscript{OC}) 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 K\textsubscript{OC} 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.

The standard assay of ecotoxicity effects studies usually provides information about the direct toxic effects of a substance. Substances showing bioaccumulation and biomagnification may pose an additional threat due to exposure of organisms higher in the food chain such as top predators. A basic assessment of the potential for bioaccumulation of a medicinal substance is given with the n-octanol/water partition coefficient (K<sub>OW</sub>). 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).

The physico-chemical and fate studies required in Phase II Tier A are listed in Table 3. Other relevant physico-chemical information (including, but not limited to, water solubility, dissociation constants, visible spectra, melting point and vapour pressure) should be transcribed from Module 2 of the MAA, presented in tabular format and cross-referenced to the relevant study reports. If available, the results of other fate studies such as ready biodegradability (OECD 301), hydrolysis (OECD 111) and photolysis should be submitted and discussed even if a Tier B assessment is not considered to be warranted.

Table 3: Physico-chemical, fate and effects studies required in Phase II Tier A

<table>
<thead>
<tr>
<th>Data requirement/test</th>
<th>Guideline to be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Octanol/Water Partition Coefficient (K&lt;sub&gt;ow&lt;/sub&gt;)</td>
<td>OECD 107 or 117</td>
</tr>
<tr>
<td>Adsorption - Desorption Using a Batch Equilibrium Method</td>
<td>OECD 106/ OECD 121/ OPPTS 835.1110*</td>
</tr>
<tr>
<td>Aerobic and Anaerobic Transformation in Aquatic Sediment Systems</td>
<td>OECD 308</td>
</tr>
<tr>
<td>Algae, Growth Inhibition Test</td>
<td>OECD 201</td>
</tr>
<tr>
<td>Daphnia sp. Reproduction Test</td>
<td>OECD 211</td>
</tr>
<tr>
<td>Fish, Early Life Stage Test</td>
<td>OECD 210</td>
</tr>
<tr>
<td>Activated Sludge, Respiration Inhibition Test</td>
<td>OECD 209</td>
</tr>
</tbody>
</table>

* All three methods are possible. However, the method used should be justified.

5.1.2 Tier A aquatic effects studies

For the Tier A assessment approach, a standard long-term toxicity test set on fish, daphnia and algae should be used to determine the PNEC<sub>WATER</sub>. The lowest value of the respective NOECs should be used for risk characterisation. The Applicant should justify the test species used. Short-term testing is generally not applicable for human pharmaceuticals since continuous exposure of the aquatic environment via STP effluents is assumed.

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

Microbial communities may be affected by the active substances of medicinal products, particularly of those designed to inhibit the growth of pathogenic microorganisms. 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\text{MICROORGANISM}, which is compared to the initial PEC\text{SURFACEWATER}.

5.1.3 Calculation of PNEC using assessment factors

The Predicted No Effect Concentration (PNEC) is calculated by applying an assessment factor to the values resulting from tests on environmental organisms from the compartment of concern, i.e. 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’.

To calculate the PNEC from the long-term toxicity tests and the microbial effect study an assessment factor of 10 is applied. This assessment factor accounts for:

- 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 PNEC\text{WATER} is based on the lowest result from the base set long-term toxicity tests. The PNEC\text{MICROORGANISM} is based on the result of the microbial effect study. The PNEC\text{GROUNDWATER} is based on the result of the *Daphnia sp.*.

5.1.4 Groundwater assessment

An exposure assessment for groundwater is required. Entry into the groundwater is considered via bank filtration. A simple estimation is PEC\text{INTERSTITIAL-WATER} = PEC\text{GROUNDWATER} in accordance with the TGD. The PEC\text{GROUNDWATER} should be compared to the PNEC\text{GROUNDWATER}.

5.1.5 Refinement of PEC\text{SURFACEWATER} in Tier A

In Tier A the PEC\text{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 the estimated patient population (from e.g. health care statistics and/or epidemiological data) supplied by the applicant.

The market penetration factor is calculated as follows.

$$F_{pen} = \frac{CONai \times 100}{DOSEai \times inhabitants \times 365 \text{ d/a}}$$
Table 4: Calculation of Fpen

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estimated consumption of active substance in geographic region per year based on statistics and/or epidemiological studies</td>
<td>CONai</td>
<td>[mg a⁻¹]</td>
<td>Normally: figures per country or regions</td>
</tr>
<tr>
<td>• Maximum daily dose of active substance consumed per inhabitant</td>
<td>DOSEai</td>
<td>[mg inh⁻¹d⁻¹]</td>
<td></td>
</tr>
<tr>
<td>• Inhabitants in geographic area</td>
<td>inhabitants</td>
<td>[inh]</td>
<td>Normally: inhabitants of countries or regions</td>
</tr>
<tr>
<td>Output</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Percentage of market penetration</td>
<td>Fpen</td>
<td>[%]</td>
<td></td>
</tr>
</tbody>
</table>

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 long-term toxicity data for algae, Daphnia and fish, data on microbial inhibition and information on the biodegradability, the persistence, the log KOW and the rate of adsorption (KOC). The PECSURFACEWATER has been refined with information on the sales forecast of the product.

- If the ratio PECSURFACEWATER : PNEC WATER for the active substance 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 active substance and/or its metabolites are unlikely to represent a risk to the aquatic environment.
- If the ratio PECSURFACEWATER : PNEC WATER is above 1, further evaluation, preferable on the fate of the active substance and/or its metabolites in the aquatic environment are needed in Tier B.
- If the ratio PECSURFACEWATER : PNECGROUNDWATER is above 1, further evaluation, preferable on the fate of the active substance and/or its metabolites in the aquatic environment are needed in Tier B.
- If the ratio PECSURFACEWATER : PNECMICROORGANISM is above 1, further evaluation of the effects of the active substance and/or its metabolites on micro-organisms are needed in Tier B.
- If the n-octanol/water partition coefficient indicates the transfer of the active substance from the aquatic environment into organisms and a potential to bioaccumulate (KOW > 1000), then the bioconcentration factor should be determined in Tier B.
- If the adsorption/desorption data indicates the affinity for the active substance to bind to sewage sludge in the STP (KOC > 10000 L/kg) an environmental assessment of the medicinal substance in the terrestrial compartment should be conducted.
- If the results from the water sediment study (OECD 308) demonstrate significant shifting of the drug substance to the sediment, effects on sediment organisms should be investigated in Tier B. The criteria for sediment studies is met if more that 10% of the substance at any time point after or at 14 days is present in sediment. A detailed strategy
for further testing in order to refine the PNEC for the aquatic compartment can be found in the TGD.

- If a compound fulfils the persistence (P) criteria (DT50 Water > 40d or DT50 SEDIMENT > 120d, OECD 308) an evaluation whether the compound fulfils the vPvB or PBT criteria should be done. Criteria for identification and guidance on the assessment of PBT and vPvB substances are set out in the TGD.

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 Specific effects on the microorganisms

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

5.3.2 Tier B Bioaccumulation

Due to the potency of medicinal products special regard should be given to the potential of bioaccumulation. If the $K_{OW}$ 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.

5.3.3 Tier B Environmental fate analysis and PEC_{SURFACEWATER} 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, surfacewater, soil) may be performed subsequently. The potential risks of the metabolites should be assessed by, at least, a bridging study investigating the toxicity of the metabolite to the taxonomic group that has been most sensitive to the parent compound in Phase II Tier A. There are no other data requirements on the fate 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, 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 ($\geq$ 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.

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adsorption of substances to sewage sludge in STPs, using the data from the estimation of the adsorption coefficient (OECD 106),

biodegradation of active substance and relevant metabolites in surfacewater, 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.

degradation with hydrolysis (OECD 111) and/or photolysis,

The local surfacewater concentration should be refined as:

\[
\text{PEC}_{\text{SURFACEWATER}} = \frac{\text{E}_{\text{local water}} \times F_{\text{stp}}}{\text{WASTEWinhab} \times \text{CAPACITY}_{\text{stp}} \times \text{FACTOR} \times \text{DILUTION}}
\]

where \( \text{E}_{\text{local water}} = \frac{\text{DOS}E_{\text{ai}} \times (F_{\text{excreta}} \times F_{\text{pen}} \times \text{CAPACITY}_{\text{stp}})}{100} \)

Table 6 summarises the parameters and default values used for the calculation of \( \text{PEC}_{\text{SURFACEWATER}} \) in Phase II. In all cases, realistic worst case estimates should be used.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
<th>Unit</th>
<th>Origin</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Input</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Maximum daily dose of active substance consumed per inhabitant</td>
<td>DOS\text{E}_{\text{ai}}</td>
<td>[mg inh(^{-1})d(^{-1})]</td>
<td>A</td>
<td>The highest recommended dose should be used.</td>
<td></td>
</tr>
<tr>
<td>- Fraction of active substance excreted</td>
<td>( F_{\text{excreta}} )</td>
<td>[%]</td>
<td>A</td>
<td>From toxicokinetic studies</td>
<td></td>
</tr>
<tr>
<td>- Amount of wastewater per inhabitant per day</td>
<td>WASTE\text{Winhab}</td>
<td>200</td>
<td>[L inh(^{-1})d(^{-1})]</td>
<td>D</td>
<td>From TGD</td>
</tr>
<tr>
<td>- Percentage of market penetration</td>
<td>( F_{\text{pen}} )</td>
<td>[%]</td>
<td>A</td>
<td>Value refined in Tier A</td>
<td></td>
</tr>
<tr>
<td>- Capacity of local sewage treatment plant (STP)</td>
<td>\text{CAPACITY}_{\text{stp}}</td>
<td>10000</td>
<td>[inh]</td>
<td>D</td>
<td>From TGD</td>
</tr>
<tr>
<td>- Fraction of emission directed to surfacewater</td>
<td>( F_{\text{stp water}} )</td>
<td>[%]</td>
<td>C</td>
<td>Calculated by SimpleTreat(TGD)</td>
<td></td>
</tr>
<tr>
<td>- Dilution factor</td>
<td>DILUTION</td>
<td>10</td>
<td>[%]</td>
<td>D</td>
<td>From TGD</td>
</tr>
</tbody>
</table>
Table 7 gives an overview on the different measures of PECSURFACEWATER refinement in the tiered step-wise risk assessment:

Table 7: Refinement of the PECSURFACEWATER

<table>
<thead>
<tr>
<th>Phase/Tier</th>
<th>Fpen</th>
<th>Fstp&lt;sub&gt;water&lt;/sub&gt;</th>
<th>Fexcreta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tier A</td>
<td>refined by applicant</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Tier B</td>
<td>refined by applicant</td>
<td>refined by SimpleTreat calculation and biodegradation test data</td>
<td>refined by toxicokinetic study</td>
</tr>
</tbody>
</table>

5.3.4 Tier B Terrestrial compartment: Environmental fate and effects testing

When indicated (KOC > 10 000 l/kg), the concentration of the medicinal product in the terrestrial compartment should be calculated. Risk assessment including PEC<sub>SOIL</sub> 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 microorganisms should be conducted (Table 8).

Table 8: Tier B Terrestrial risk assessment studies

<table>
<thead>
<tr>
<th>Data requirement/test</th>
<th>Guideline to be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobic and anaerobic transformation in soil</td>
<td>OECD 307</td>
</tr>
<tr>
<td>Soil Microorganisms: Nitrogen Transformation Test</td>
<td>OECD 216</td>
</tr>
<tr>
<td>Terrestrial Plants, Growth Test</td>
<td>OECD 208</td>
</tr>
<tr>
<td>Earthworm, Acute Toxicity Tests</td>
<td>OECD 207</td>
</tr>
<tr>
<td>Collembola reproduction</td>
<td>ISO 11267</td>
</tr>
</tbody>
</table>

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:

- An indication of potential risks presented by the medicinal product for the environment.
- Product labelling, Summary Product Characteristics (SPC), Package Leaflet (PL) 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 sewage 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 CHMP

The applicant may request scientific advice from the CHMP -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. If other relevant data are available they should also be submitted, e.g. tests focussing on relevant substance specific biological effects.

The Expert Report should include an evaluation of 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) 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 derived from a wide range of individual market penetration factors which were calculated as follows:

\[
\text{Fpen}[^\%] = \frac{\text{consumption}[\text{mg}\text{*year}^{-1}] \times 100}{\text{DDD}[\text{mg}\text{*d}^{-1}\text{*inhab}] \times \text{inhabitants}[\text{inhab}] \times 365\text{ d*year}^{-1}}
\]

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 in 2001

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.

(2) Assessment factor

The TGD assumes that each of the uncertainties arising from the extrapolation from laboratory tests to the ecosystem, make a significant and equal contribution to the overall uncertainty. The role and magnitude of these uncertainties are however not well validated [A]. Notably the relation between acute and chronic effects with the same test species will depend on the qualities of the chemical under consideration, in contrast to intra- and interspecies relations. Based on acute and chronic data averaged over all species, the ratio is found to be between 1 and 100 [B]. In an analysis of acute and chronic endpoints within single species, acute-to-chronic ratios (ACR) were highly variable, ranging from 0.79 to 5000 [C]. At least 30% of the variation in ACR could be explained by chemical class. Furthermore, there was a 100% probability that the extrapolation factor derived from the combination of ACR within species and interspecies variability based on acute data, is greater that 1000 (instead of the 100 as expected). Conceptually, based on the specific mode of actions of pharmaceuticals, i.e. modulation of receptors at sub-toxic levels, a large discrepancy between chronic effects on reproduction or individual growth, and acute effects, i.e. based on mortality or population growth rate, are to be expected. It is therefore hypothesised that an AF of 1000 on acute data will not be protective for chronic exposure.

The hypothesis is tested against the limited information on ACR available. ACR determined for diclofenac, clofibric acid and carbamazepine for the same batch of the crustacean Cerodaphnia dubia were 23, 213 and 5100 [D].
Invertebrates (C. dubia, D. magna and H. azteca) were exposed to atenolol, metoprolol, nadolol and propranolol and average invertebrate 48h LC50 ranged from 0.85-29.8 mg/L. Reproduction of H. azteca after a 27 days exposure was impacted at sublethal levels of propranolol with a NOEC of 0.001 and a LOEC of 0.1 mg/L. C. dubia reproduction NOEC and LOEC were 0.125 and 0.250 mg/L (Huggett et al., 2002). The ACR for these compounds is hence at least 850.

ACR were calculated for seven compounds by Webb [F]. Iopromide, a radiopaque medium, has an ACR of 1, as there were neither acute nor chronic effects at 1000 mg/L. The other ratios were: clofibrate 1428 in D. magna, etidronic acid 44 in D. magna; nicotine 43 in D. pulex, and the metabolite salicilic acid 6 in D. magna.

The ACR for endocrine disrupting agents may be in orders of magnitude: for diethylstilbestrol and ethynilestradiol in D. magna 17.6 and 570, but in O.mykiss the ACR for ethynilestradiol is 800,000 [F].

These limited data substantiate rather than refute the hypothesis that an AF of 1000 on acute data will not be protective for pharmaceuticals. Ferrari et al. (2004) recently reached the same conclusion based on similar data [G].

It is therefore considered justified not to base the PNEC on acute, but rather on chronic data. Without special indications a base set consisting of an algae growth rate inhibition test, a Daphnid reproduction test, and a fish early life stage test would be required.

Full life cycle testing of invertebrates and fish may be required for specific compounds, e.g. with possible endocrine disrupting properties. For fish the OPPTS 850.1500 [H][I] or the OECD two generation test [J] can be considered. For invertebrates a full life cycle test with marine mysid shrimps could be considered supplementary to the Daphnid test [K,L,M]


10. LIST OF ABBREVIATIONS

ACR  Acute to chronic ratio
AF   Assessment Factor
BCF  Bioconcentration Factor
CFC  Chlorofluorocarbons
CHMP Committee for Human Medicinal Products
DDD  Defined daily dose value(s)
DT50 Degradation half life
EC50 Effective Concentration 50%
EMEA European Medicines Agency
ERA  Environmental Risk Assessment
FDA  United States Food and Drug Administration
GLP  Good Laboratory Practice
GMO  Genetically Modified Organism
ISO  International Organization for Standardization
Koc  Adsorption Coefficient
LC50 Lethal Concentration 50%
LOEC Lowest Observed Effect Concentration
MAA  Marketing Authorisation Application
NOEC No Observed Effect Concentration
OECD Organization for Economic Co-operation and Development
PBT  Persistent, Bioaccumulative and Toxic
PEC  Predicted Environmental Concentration
PNEC Predicted No Effect Concentration
PL   Package Leaflet
SPC  Summary of Product Characteristics
STP  Sewage Treatment Plant
TGD  Technical Guidance Documents
vPvB Very persistent and bioaccumulative
11. REFERENCES

- Dietrich D. 2002. Special Issue on pharmaceuticals in the environment. Toxicology Letters 131:
- Jorgensen SE, Halling-Sørensen B. 2000. Special issue on pharmaceuticals in the environment. Chemosphere 40:
12. ANNEX

Figure 2: Entry paths of human medicinal products into the environment
13. DECISION TREE

Phase I
- Exposure estimate for the parent compound, or the active metabolite for pro-drugs based on formula given in 4.1 - Phase I Calculation of the Predicted Environmental Concentration (PEC).
- Substances such as vitamins, electrolytes, amino acids, peptides and proteins can be exempted from testing because they are unlikely to result in significant exposure of the environment and will consequently be of low environmental risk

Action limit
- If the PEC > 0.01 µg/L a Phase II risk assessment should be conducted, if the PEC < 0.01 µg/L the assessment stops. However, substances which may affect the environment at concentrations below the action limit advance to Phase II irrespectively of the PEC.

Phase II Tier A Base data set

<table>
<thead>
<tr>
<th>Data requirement</th>
<th>Guideline to be used</th>
<th>Data requirement</th>
<th>Guideline to be used</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Octanol/Water Partition (Kow)</td>
<td>OECD 107 or 117</td>
<td>Alga, Growth Inhibition Test</td>
<td>OECD 201</td>
</tr>
<tr>
<td>Adsorption - Desorption Using a Batch Equilibrium Method</td>
<td>OECD 106/ OECD 121/ OPPTS 835.1110*</td>
<td>Daphnia sp. Reproduction Test</td>
<td>OECD 211</td>
</tr>
<tr>
<td>Aerobic and Anaerobic Transformation in Aquatic Sediment Systems</td>
<td>OECD 308</td>
<td>Fish, Early Life Stage Test</td>
<td>OECD 210</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Activated Sludge, Respiration</td>
<td>OECD 209</td>
</tr>
</tbody>
</table>

Phase II Tier A Assessment

<table>
<thead>
<tr>
<th>Hazard/Risk assessment</th>
<th>Criterion*</th>
<th>Data requirement/Assessment approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Octanol/Water Partition (Kow)</td>
<td>Log $K_{OW} \geq 3$</td>
<td>BCF study (OECD 305), See EU.TGDs for assessment of bioaccumulation and magnification</td>
</tr>
<tr>
<td>Aerobic and Anaerobic Transformation in Aquatic Sediment Systems ($DT_{50}$)</td>
<td>$DT_{50,\text{Wahi}} &gt; 40d/60d^2$ $DT_{50,\text{SEDIMENT}} &gt; 120d^2/180d^2$</td>
<td>If P of PBT or $vPvB$ criteria are met, check B and T criteria, if applicable, follow the EU-TGDs approach.</td>
</tr>
<tr>
<td></td>
<td>$&gt; 10%$ in sediment at day 14 or later</td>
<td>Sediment organism effects study</td>
</tr>
<tr>
<td>Adsorption - Desorption (KOC)</td>
<td>Log $K_{OC} \geq 4$</td>
<td>Calculate PEC_{SOC}. Terrestrial assessment studies are OECD 307, 216, 208, 207, ISO 11267. Risk characterisation with lowest PNEC of terrestrial effects tests.</td>
</tr>
</tbody>
</table>

PECSURFACEWATER is refined in accordance with chapter 5.1. Risk characterisation for PNEC based on aquatic base data set and microorganisms only, respectively.

PECSURFACEWATER is refined in accordance with chapter 5.1. Risk characterisation for groundwater with PNEC based on $Daphnia$.

PECWGROUNDCWATER $\geq 1$
PEC/PNEC_{GROUNDWATER} $\geq 1$

Refine the PEC with data on degradation/retention in the STP, data on metabolism in the patient, data on degradation in the environment. In case PEC refinement is based on transformation in the patient/environment and metabolites $> 10\%$ are formed, then effects studies for these metabolites should be submitted to allow for refinement. For microorganisms, additional effects data may refine the PNEC.

* If a criterion is not met, then the Tier B assessment for this criterion can be waived, 'PBT criterion, 'vPvB criterion