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Guideline on the environmental risk assessment of medicinal products for human use

Draft

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This guideline replaces 'Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr 2)'.

Comments should be provided using this template. The completed comments form should be sent to ERA_DG@ema.europa.eu

Keywords	***Environmental risk assessment, ERA, Human medicinal products, PBT***

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Guideline on the environmental risk assessment of medicinal products for human use

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Executive summary

The purpose of this guideline is to describe the assessment of the potential environmental risks and hazards of human medicinal products (HMP). It specifies the scope and legal basis for assessment. It outlines general considerations and the recommended step-wise procedure of assessment. The general outline of the Environmental Risk Assessment Report is included, and for products for which risks cannot be excluded, this guideline outlines the possible precautionary and safety measures.

1. Introduction (background)

It is mandatory for the dossier for the marketing authorisation of HMP to include an environmental risk assessment (ERA). This ERA is based on the use of the product and the physico-chemical, ecotoxicological, and fate properties of its active substance. This guideline describes how to perform this ERA and how to evaluate potential risks to the environment arising from the use of the medicinal product, with the aim of protecting aquatic and terrestrial ecosystems including surface water, groundwater, soil and secondary poisoning - and the microbial community in sewage treatment plants. Furthermore, the identification of potential hazards of the active substance of a medicinal product is described. The guideline also includes consideration of potential precautionary and risk mitigation measures, and provides guidance on how to report the findings in an Environmental Risk Assessment Report.

2. Scope and legal basis

In accordance with Article 8(3) of Directive 2001/83/EC, as amended, the evaluation of the potential environmental risks posed by the use of medicinal products shall be submitted, their environmental impact shall be assessed and, on a case-by-case basis, specific arrangements to limit this impact shall be considered. However, in any event this impact should not constitute a criterion for refusal of a marketing authorisation.

An ERA is required for all new marketing authorisation applications for a medicinal product through a centralised, mutual recognition, decentralised or national procedure.

For type II variations, the ERA dossier should be updated if there is an anticipated increase in the environmental exposure, e.g. a new indication which results in an increase in the extent of the use. For extension applications according to Annex II of Commission Regulation (EC) No 1085/2003, ERA is also required if there is an anticipated increase in the environmental exposure, e.g. an extension application of an oral medicinal product to include a dermal patch. The environmental data previously submitted in the original dossier of the same marketing authorization holder (MAH) may serve as a basis for the revised ERA for the variation or extension application.

An ERA is not required for renewals of marketing authorisations or Type IA/IB variations. For further details, please refer to the Agency's pre-authorisation guidance, Q&A No 3.4.2.

According to Directive 2001/83/EC, applicants are required to submit an ERA irrespective of the legal basis. Generic medicinal products are therefore not exempted from providing an ERA. However, cross reference to the ERA dossier of the originator is permitted with consent from the originator.

This guideline does not apply to medicinal products consisting of genetically modified organisms (GMOs). Applicants are referred to the guideline on "Environmental Risk Assessment for Human Medicinal Products containing, or consisting of, genetically modified organisms (GMOs) (Module 1.6.2) (EMEA/CHMP/473191/06 - Corr)".

For marketing authorisation applications for radio-pharmaceutical precursors for radio-labelling and radio-pharmaceuticals, additional requirements on emission standards for radiation set by Council Directives 2013/59/Euratom should be taken into account.

Excipients do not generally require an ERA unless there is a specific toxicological effect to suggest an environmental risk under the product's conditions of use.

3. General Principles

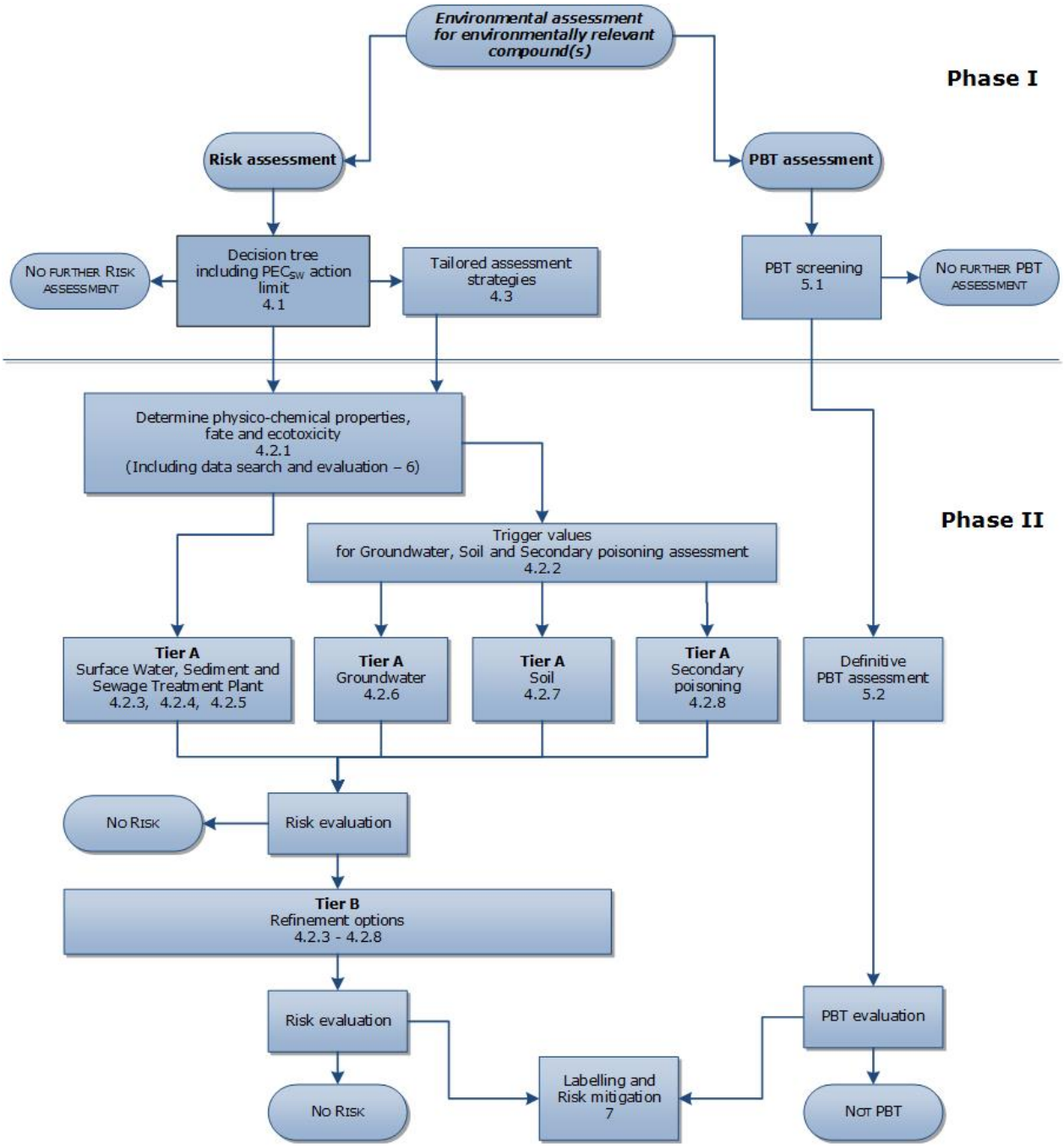
3.1. Overview of the risk assessment and PBT assessment

For each medicinal product, both a risk assessment and a specific hazard assessment for persistent, bioaccumulative and toxic (PBT) properties is required (see Figure 1). The risk assessment reflects the possibility of an effect occurring, and is an evaluation of both exposure of organisms in the environment to the active substance and ecotoxicity. For some substances with specific classifications (e.g. endocrine active substances (EAS), antibiotic substances), a tailored risk assessment is necessary. The PBT assessment concerns the intrinsic properties of a specific group of active substances, which are potentially harmful to the environment regardless of the levels of exposure. Active substances that do not degrade well in the environment (persistent), accumulate in organisms (bioaccumulative), and are toxic, are identified in the PBT/vPvB (very persistent and very bioaccumulative) assessment.

The ERA may consist of a justification for not submitting ERA studies. However, this only applies to certain cases which are specified in section 4.1 and 5.1.

In the interest of animal welfare the principles of 3Rs (Replacement, Reduction and Refinement) in accordance with Directive 2010/63/EU should be implemented whenever possible.

Figure 1: Overview of the environmental risk and PBT assessment including references to section numbers in the main text.



3.1.1. Risk assessment

In Phase I, a decision tree (**Figure 2**, section 4.1) is followed to identify the products that require a Phase II assessment. The Phase I decision tree concludes with the calculation of a Predicted Environmental Concentration in surface water (PEC_{SW}), based on the predicted use of the product. When this PEC is ≥ the action limit of 0.01 µg/L, a Phase II assessment (section 4.2) should be performed. Some substances (e.g. endocrine active substances and antiparasitics) should enter Phase II regardless of their PEC value (see decision tree, **Figure 2**), because they may affect organisms in the environment at concentrations < 0.01 µg/L.

The Phase II risk assessment starts with studies on physico-chemical properties, and on the environmental fate and ecotoxicological effects of the active substance. For some groups of substances, a tailored risk assessment strategy should be followed that addresses their specific mechanism of action (section 4.3). In Tier A, the PEC is compared to an acceptable environmental concentration, the Predicted No Effect Concentration (PNEC). When a risk is identified in Tier A, a Tier B assessment with PEC refinement and if warranted further effect studies should be performed.

The studies that should be performed in Phase II Tier A on physico-chemical characteristics, fate and ecotoxicity are described in section 4.2.1. The requirement for a risk assessment for certain environmental compartments (soil and groundwater) depends on whether trigger values are met by the outcome of these studies. Information on data search and evaluation is provided in section 6.

The Phase II risk assessment for the surface water compartment including options for risk refinement is described in section 4.2.3. Sections 4.2.4. - 4.2.7. give guidance on Phase II risk assessment and risk refinement for sediment, functioning of sewage treatment plants (STP), soil and groundwater, respectively. The assessment of risk to predators eating contaminated prey (secondary poisoning) is described in section 4.2.8.

3.1.2. PBT assessment

The PBT (Persistent, Bioaccumulative and Toxic) assessment concerns the identification of certain intrinsic properties of the active substance. These properties make the long-term risks to the environment unpredictable; hence environmental exposure should be prevented as much as possible. As the PBT assessment concerns intrinsic properties of the active substance subsequent exposure is not considered. The assessment of PBT and vPvB properties is described in section 5. Compounds entering the screening phase (section 5.1) are identified in the first part of the decision tree (Question 1-3). Depending on the outcome of the screening phase, a definitive assessment may be required. (section 5.2).

In exceptional cases for substances which do not meet the trigger for PBT assessment (log Kow > 4.5) an assessment of PBT/vPvB properties may be required. This will be the case if the results obtained in Phase II of the risk assessment demonstrate that the B- and T-criteria are met, or if the vB-criteria is met (see **Table 16**).

3.1.3. Finalization of risk and PBT assessment

When a risk is identified and/or a substance is classified as PBT/vPvB, this information should be included in the SmPC and risk mitigation measures should be discussed. These are described in section 7.

The structure of the risk assessment report is described in section 8.

3.2. General considerations

The ERA should be performed for the environmentally relevant chemical species, which in most cases is the parent compound.

3.2.1. Total residue approach

The ERA is based on a 'total residue approach', i.e. the assumption that the active substance is completely excreted as parent substance without metabolism or assuming that metabolites have similar or lower toxicity than that of the parent substance.

Metabolism of the active substance may be taken into account in Phase II, see section 4.2.3.2.

For a **prodrug**, the most environmentally relevant substance will generally be the pharmacologically active metabolite. However, there may be instances where a prodrug is incompletely converted to the active (<50%), or excreted largely (>50%) intact or via metabolic pathways that do not generate the active moiety. In these cases, the selection of the environmentally relevant chemical species should be justified. In some cases, assessment of both prodrug and active may be necessary.

For **fixed combination products**, the ERA is performed separately for each compound within the product.

3.2.2. Test guidelines

Experimental studies performed by or on behalf of the applicant should be GLP-compliant and preferably follow the most recent test guidelines issued by the Organization for Economic Co-operation and Development (OECD) or comparable international validated test guidelines. QSARs (Quantitative Structure-Activity Relationships) and read-across cannot replace the studies requested in this guideline.

A number of methods used in this guideline are based on methods described in the REACH (e.g. ECHA, 2016; ECHA, 2017a-d) and Water Framework Directive EQS (European Communities, 2011) guidelines, as well as OECD guidance documents and technical guidelines. In case of future revisions of these guidelines, the revised version of the relevant method or test guideline should be used.

3.2.3. Publicly available data

For active substances that are already marketed, information may be available in the public domain. To prevent repetition of (animal) studies and allow identification of signals emerging from environmental monitoring and research, the Applicant should provide a complete literature review (See section 6.1 on data search). When other marketing authorisation holders have already performed relevant studies, they are encouraged to share data with the Applicant, in order to minimise the number of tests having to be re-performed. Public Assessment Reports (PARs and EPARs) and reviews or summary data from other regulatory frameworks cannot be used in the ERA dossier without the underlying study reports. All data submitted (whether study reports or peer reviewed literature) should contain enough information to permit assessment of the reliability of the study performed (See section 6.2 on evaluation of studies).

4. Risk Assessment

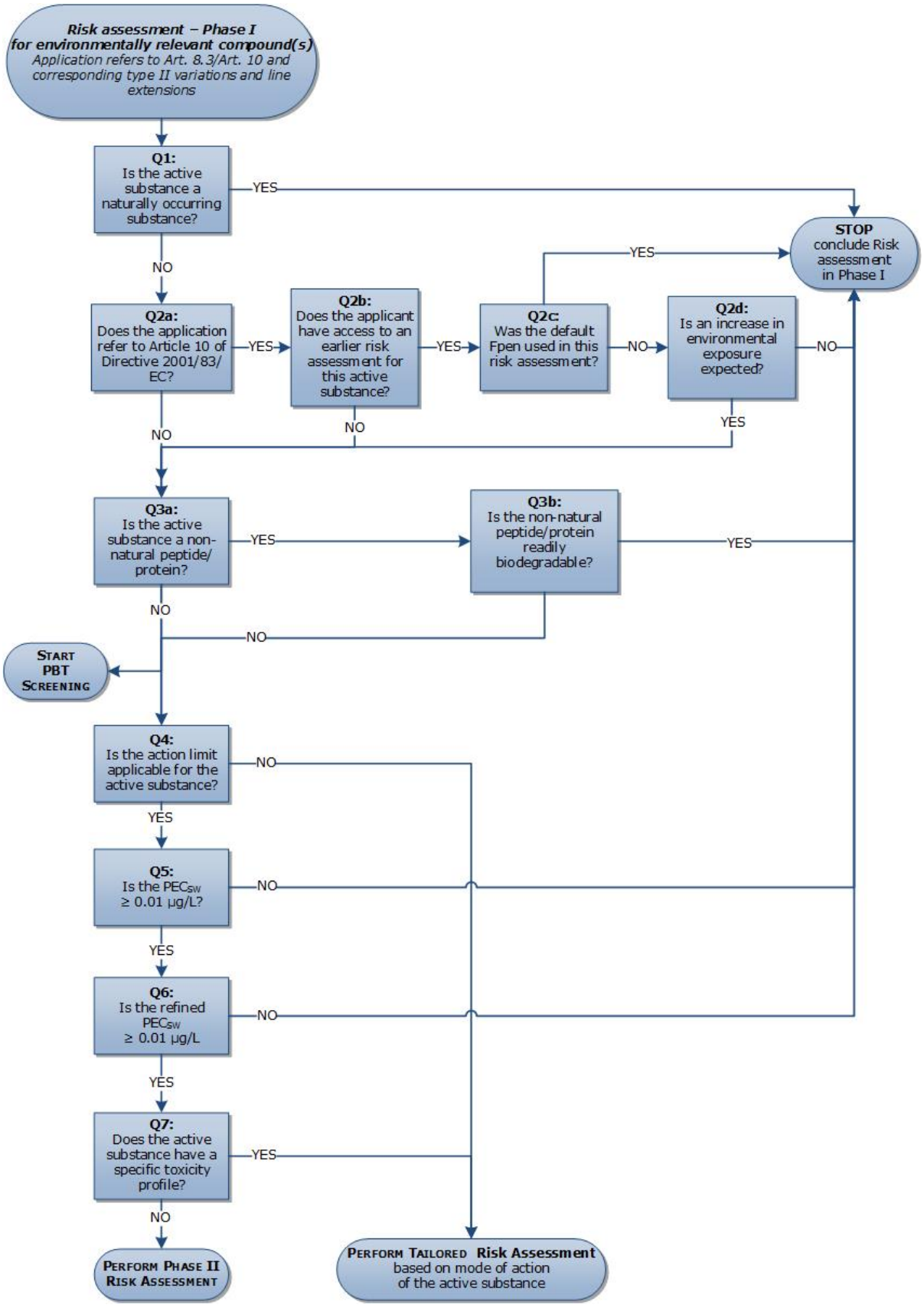
4.1. Phase I Risk Assessment

This section presents guidance on how to conduct the Phase I risk assessment. The potential for environmental exposure is assessed based on the nature of the active substance and the intended use. In Phase I, products that require a more extensive Phase II risk assessment – either standard or tailored - are identified. It is assumed that active substances with limited use and/or limited environmental exposure will have limited environmental effects, and thus the risk assessment will stop in Phase I.

The Phase I risk assessment consists of a decision tree (**Figure 2**). The questions in the decision tree are described in detail below **Figure 2**. The outcome of Phase I may be that the risk assessment stops, or that a Phase II risk assessment is required. When at least one of the Phase I criteria to stop the risk

210 assessment has been met, the applicant should produce a report on the ERA, discussing the basis for
211 the decision.

212 **Figure 2: Phase I Decision tree (Q: question)**



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Questions in Phase I Decision tree (Figure 2):

Q1: Is the active substance a naturally occurring substance?

In the case of medicinal products comprised of naturally occurring substances such as vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates and lipids as active pharmaceutical ingredient(s) (API), the ERA may consist of a justification for not submitting ERA studies, e.g. that due to the physico-chemical nature of the API these products are unlikely to pose a risk to the environment or based on the environmental fate and/or common presence in the environment these products are unlikely to alter the concentration or distribution of the substance in the environment.

The same criteria applies to herbal medicinal products as defined in Directive 2004/24/EC. However, there may be exceptional cases where further justification for the absence of studies might be necessary, e.g., when a compound is classified as being a carcinogen, mutagen, or toxic for reproduction (CMR) or PBT (see section 5), or if a risk has been identified in another framework.

Vaccines are unlikely to result in a risk to the environment and the ERA may consist of a justification for not submitting ERA studies. Adjuvants contained in vaccines may however require additional justification for the absence of ERA studies according to the principles outlined above.

Q2a: Does the application refer to Article 10 of Directive 2001/83 EC as amended?

According to Directive 2001/83/EC as amended, applicants are also required to submit an ERA for applications under Art 10(1) and 10(2) -generic medicinal products, Art 10(3)-hybrid, Art 10a-well established use/bibliographical, Art 10b fixed combinations, Art 10c informed consent and Art 10(4) similar biological applications.

Q2b: Does the applicant have access to an earlier ERA for the active substance?

In order to avoid unnecessary repetition of studies, and in particular animal studies, applicants are encouraged to share their data. If the current applicant has access to an ERA that was performed earlier by another marketing authorisation holder, this ERA (including study reports) may be submitted, including a letter of access. If the reference ERA is not complete in accordance with the current guideline (e.g. studies are missing, or increased environmental exposure may be anticipated) the applicant should conduct the missing studies and/or update the ERA.

Q2c: Was the default market penetration factor (Fpen) used in this risk assessment?

If the default Fpen (0.01) was used in this earlier risk assessment, and provided that the indication is the same, the outcome of the risk assessment will not change and the risk assessment stops. However, if a refined Fpen was used, this Fpen may change and thus the outcome of the risk assessment may change.

Q2d: Is an increase in environmental exposure expected?

An increase in environmental exposure may be expected when e.g., a new indication or a new patient population is added, the maximum daily dose is increased, a new route of administration or a new pharmaceutical form is added or a marketing authorisation is applied for in a member state with a higher prevalence of the disease. If a refined Fpen was used in the previous ERA, an applicant applying for a marketing authorization in a new member state should compare the prevalence in this new member state with the prevalence used to refine Fpen in the previous ERA. If the environmental exposure for any reason is increased compared to the environmental exposure used in the previous ERA, the ERA should be updated accordingly.

Q3a: Is the active substance a non-natural peptide / protein?

Peptides and proteins that have been structurally modified using non-natural amino acids to increase biostability are considered non-natural.

Protein-drug conjugates including natural proteins do not belong to this group and would require standard assessment of the non-protein-moiety.

Q3b: Is the non-natural peptide / protein readily biodegradable?

For non-natural peptides/proteins, an additional screening step should be performed to demonstrate that they will be quickly degraded in the environment and will not enter the STP.

When the non-natural peptide/protein is demonstrated to be excreted in amounts < 10% of the dose, or shown to be readily biodegradable in an OECD 301 test, the ERA stops.

Q4: Is the PEC_{SW} action limit of 0.01 µg / L applicable for the active substance?

For active substances that can affect environmental organisms at concentrations < 0.01 µg/L, the action limit may not be applicable. Examples include endocrine active substances (EAS) and antiparasitics. For EAS, a tailored risk assessment is required. More information on identification and tailoring of studies for EAS and other specific active substances can be found in section 4.3.

Q5: Is the PEC_{SW} ≥ 0.01 µg/L?

In Phase I, the predicted environmental concentration (PEC) calculation is restricted to the surface water compartment. The PEC_{SW} is calculated using default values and the following assumptions:

- 1% of a population receive the active substance daily.
- The sewage system is the main route of entry of the active substance into the surface water.
- There is no biodegradation or retention of the active substance in the sewage treatment plant (STP).
- There is no metabolism in the patient.

The PEC_{SW} concentration can be calculated using the following formula in Equation 1:

$$PEC_{SW} = \frac{DOSE_{AS} \times F_{PEN}}{WASTEW_{INHAB} \times DILUTION} \qquad \textbf{Eq. 1}$$

Parameters used in Eq 1:

Parameter	Description	Unit	Default value
PEC_{SW}	Predicted environmental concentration for surface water calculated in Phase I	[mg L^{-1}]	-
$DOSE_{AS}$	Maximum daily dose of the active substance consumed per inhabitant	[mg inh^{-1} d^{-1}]	-
F_{PEN}	Fraction of a population receiving the active substance	[--]	0.01
$WASTEW_{INHAB}$	Amount of wastewater per inhabitant per day	[L $inh^{-1}d^{-1}$]	200
DILUTION	Dilution factor	[--]	10

If the PEC_{SW} value is < 0.01 µg/L and no other environmental concerns are apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients and no further risk assessment is required.

Q6: Is the refined PEC_{SW} ≥ 0.01 µg/L?

PEC_{SW} may be refined by refining the F_{PEN} value based on prevalence data and/or based on the treatment regimen. For medicinal products, which can be used for more than one indication, the calculation of refined PEC_{SW} should take into account all designated indications for the product. The total PEC_{SW} is the sum of the PEC_{SW} for each indication, which should be calculated using the maximum prescribed dose for each indication. The other default values representing a realistic worst case environmental exposure scenario should not be replaced by other data. If the refined PEC_{SW} value is < 0.01 µg/L, and no other environmental concerns are apparent (e.g. the compound is a potential EAS or paraciticide), it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients and no further risk assessment is required.

Prevalence: The F_{PEN} can be refined by submitting European disease prevalence data for the sought indication(s). Such data should be published by a reliable and independent source, e.g. a peer-reviewed scientific journal or the World Health Organization (WHO) (e.g., the International Agency for Research on Cancer (IARC)). It is assumed that 100% of the patient population is taking the medicinal product for the relevant disease(s) daily and thus the F_{pen} reflects the prevalence of the disease. If regional differences exist, the F_{PEN} should be calculated for the member state or region with the highest prevalence of the disease. This member state should be one of the member states included in the authorisation procedure. Prevalence data at subnational level (i.e. for regions smaller than a country) can also be used in the risk assessment, provided they are of good quality as described above and justification for use in the risk assessment is provided. Prevalence data should be as recent as possible, preferably not older than 5 years. The use of older data should be justified. For orphan drug submissions, the F_{PEN} can be refined based on the prevalence for which the medicinal orphan drug designation was based, as adopted by the Committee for Orphan Medicinal Product (COMP). One year prevalence data should be used unless other prevalence data (e.g. multiple year prevalence, lifetime prevalence or incidence if appropriate) can be justified considering epidemiologic and posology data available for the supported indication.

Treatment regimen: The F_{PEN} may be refined taking the worst-case treatment period ($t_{TREATMENT}$) and worst-case number of treatment repetitions per year ($n_{TREATMENT}$) into consideration. This is easily done for products intended for single use (e.g. during surgery, diagnostics, etc.) or other products with a well-defined treatment regimen. For example, an anti-cancer drug administered for five days in monthly cycles, $t_{TREATMENT}$ equals 5 days and $n_{TREATMENT}$ would be 12 $year^{-1}$. The posology should be clearly reflected in the SmPC. For other treatment patterns, F_{pen} refinement based on an intermittent treatment regimen should be based on clinical considerations and justified by a reliable and independent source. In exceptional cases, refinement based on clinical considerations is possible without the presence of public literature. This is only acceptable if these clinical considerations are well-described and based on clinical data in the dossier; for instance, in the case of anti-cancer treatment with a maximum number of treatments per year (e.g. once every 3 weeks) where severe adverse effects prevent an increase in treatment regimen. Refinement based on treatment regimen is not justified for pharmaceuticals dosed 'as needed' unless this is based on published scientific literature.

The following approach may be used for the refinement of F_{PEN} by prevalence data and /or by treatment regimen:

$$F_{PEN-REFINED} = \frac{P_{REGION} \times t_{TREATMENT} \times n_{TREATMENT}}{Nd} \qquad \textbf{Eq. 2}$$

330

331 The $F_{PEN\ REFINED}$ should be used for the calculation of refined PEC_{SW} using Equation 3:

332

$$PEC_{SW} = \frac{DOSE_{AS} \times F_{PEN-REFINED}}{WASTEW_{INHAB} \times DILUTION} \qquad \textbf{Eq. 3}$$

333

334 Parameters used in Eq.2 and 3:

Parameter	Description	Unit	Default value
$F_{PEN\text{-}REFINED}$	Refined fraction of a population receiving the active substance during a given time	[--]	
P_{REGION}	Prevalence for the region with the highest prevalence, as described above	[--]	
$t_{TREATMENT}$	Duration of one treatment period	[d]	
$n_{TREATMENT}$	Number of treatments per year	[yr^{-1}]	
Nd	Number of days per year	[d yr^{-1}]	365
PEC_{SW}	Predicted environmental concentration in surface water based on $F_{PEN\ REFINED}$	[mg L^{-1}]	
$DOSE_{AS}$	Maximum daily dose of the active substance consumed per inhabitant	[mg inh^{-1} d^{-1}]	
$WASTEW_{INHAB}$	Amount of wastewater per inhabitant per day	[L $inh^{-1}d^{-1}$]	200
DILUTION	Dilution factor	[--]	10

335

336 If the PEC_{SW} value based on a refined F_{PEN} is < 0.01 µg/L, and no other environmental concerns are
337 apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment
338 following its prescribed usage in patients and no further risk assessment is required.

339 **Q7: Does the active substance have a specific toxicity profile?**

340 A tailored risk assessment is needed for compounds with a specific mode of action (e.g., endocrine
341 active substances, antibiotics), see section 4.3.

342 *4.2. Phase II Risk Assessment*

343 4.2.1. Determination of physico-chemical properties, fate and ecotoxicity

344 Physico-chemical properties of active substances are important drivers for fate and toxicity. The
345 determination of some of these properties is therefore mandatory for the assessment. **Table 1** gives
346 an overview of the mandatory and non-mandatory studies on physico-chemical properties, fate and
347 ecotoxicity. This base set of data cannot be omitted even if studies such as OECD 303A and OECD
348 314B show degradation in sewage treatment plants (STPs), because the availability of STPs varies
349 across Europe and removal efficiencies for pharmaceuticals vary considerably. A description of the
350 studies is provided below.

Experimental studies should preferably follow the test guidelines issued by the OECD or the European Commission. It is recognised that there are other test guidelines, approaches and methods, which are capable of providing an equivalent environmental risk assessment. If methods other than those described in this section are used, a justification should be included in the Environmental Risk Assessment Report.

Table 1: Studies to be performed for Phase II Tier A assessment

Study	**Guideline**
Physico-chemical properties (4.2.1.1)	
Water solubility	OECD 105
Octanol/Water Partitioning (#)	OECD 107 or 123
Dissociation in Water	OECD 112
UV-Visible Absorption Spectrum (*)	OECD 101
Melting Point/Melting Range (*)	OECD 102
Vapour Pressure (*)	OECD 104
Fate properties (4.2.1.2)	
Adsorption - Desorption Using a Batch Equilibrium Method with 3 soils and 2 sludges	OECD 106
Ready Biodegradability Test	OECD 301
Aquatic toxicity (4.2.1.3)	
Algae, growth inhibition	OECD201
Daphnia sp. reproduction	OECD 211
Fish, Early life stage toxicity	OECD 210
Functioning of STP (4.2.5.1)	
Activated sludge, respiration inhibition	OECD 209
Sediment toxicity (choose one of the tests below) (4.2.1.3)	
Lumbriculus sp., spiked sediment	OECD 225
Chironomus, sediment-water toxicity	OECD 218/219
Chironomus, sediment-water life-cycle toxicity	OECD 233

(*) Not mandatory.
(#) Study also requested for Phase I PBT screening.

4.2.1.1. Physico-chemical characteristics

Water solubility

The solubility of the active substance should be determined experimentally, using the most appropriate method according to the OECD 105 test guideline. For dissociating compounds, the test should be performed at pH 5, 7 and 9. The results of this test are used to verify exposure concentrations in fate and ecotoxicity tests. Additionally, solubility should be compared to the octanol/water partitioning value, to evaluate the plausibility of the results.

Octanol / water partitioning coefficient (Kow)

The octanol/water partitioning coefficient, Kow, should be determined experimentally using the shake-flask method (OECD 107) or the slow-stirring method (OECD 123). A calculated value is generally not acceptable. The results from the HPLC screening method (OECD 117) may only be used for indicative purposes, e.g. for compounds, which are highly soluble and have a predicted log Kow < 1 at all environmentally relevant pH values.

For compounds with log Kow > 4, the shake-flask method cannot be used and only the slow - stirring method is acceptable. This range of applicability is based on OECD guidelines 123 and 107.

For dissociating compounds, an ion-corrected log Dow for the neutral molecule should be reported together with the respective pKa value(s). The ion-corrected Dow is equal to Kow.

Log Dow values should be determined as a function of pH covering an environmentally relevant pH-range (at least 3 pH values ranging from pH 5 to 9) e.g. by measuring the pH-lipophilicity profile (log D as function of pH). If the Dow value (for dissociating substances) at any pH value between pH 5 and pH 9 meets the trigger values for assessment of secondary poisoning (log Kow ≥ 3) or PBT assessment (log Kow > 4.5), further assessment is required (see Section 4.2.8 and 5).

Dissociation constant

The dissociation constant should be determined for dissociating compounds. The results of this study are used to verify exposure concentrations in fate and ecotoxicity tests. Additionally, the information is required to determine the octanol/water partitioning coefficient.

4.2.1.2. Fate studies

Along with mandatory studies on physico-chemical properties, mandatory fate studies should be included in the ERA in order to evaluate the fate and predict the environmental exposure of the medicinal product. These mandatory studies are listed in **Table 1**.

Sorption to soil and sludge

Adsorption/desorption studies generate essential information on the mobility of the active substance and its distribution in the soil and water compartments. This is a complex process depending on many factors including chemical properties, characteristics of the soil and climatic factors. Therefore, different sludge and soil types should be used in order to cover as widely as possible the interactions of the active ingredient with sludge and soils.

A study according to OECD 106 using 2 types of sludge and 3 soil types, differing in organic carbon content, and soil texture is preferred. The results are used to evaluate the requirement for soil and groundwater assessment (section 4.2.2) and to perform PEC calculations for soil and sediment in Phase II Tier A. In Phase II Tier B, adsorption data for at least 2 types of sludge, preferably from two different STPs are necessary for PEC_{SW} refinement (SimpleTreat modelling, section 4.2.3.2). Adsorption data for at least 3 soils are needed for equilibrium partitioning calculations in the sediment risk assessment (Section 4.2.4) and refinement of PEC_{GW} in Tier B (section 4.2.6.2). An overview of Phase II risk assessment steps where adsorption data are needed is listed in **Table 2** below.

The targeted endpoint for adsorption studies should be the distribution coefficient (Kd), defined as the ratio between the content of the substance in the soil/sludge phase and the mass concentration of the substance in the aqueous solution, under the test conditions, when adsorption equilibrium is reached. The organic carbon normalized adsorption coefficient (Koc) relates the distribution coefficient Kd to the organic carbon content of the soil sample.

409 **Table 2:** Use of adsorption data in Phase II risk assessment

Adsorption needed in Phase II	Tier A	Tier B
Surface water	Not needed	SimpleTreat - Input: lowest Koc_{SLUDGE}* for partition coefficient in raw sewage (Kp_S) and activated sludge (Kp_{AS}) Refined PEC_{SW}-calculation: Lowest Koc_{SOIL} for FACTOR (sorption on suspended matter in surface water)
Sediment	PEC_{SED}-calculation: K_{SUSP_WATER} with highest Koc_{SOIL}**	Not needed
Groundwater	Trigger: lowest Koc_{SLUDGE}*	SimBaFi - Input: lowest Kd_{SOIL} **
Soil	Trigger: highest Koc_{SLUDGE}* SimpleTreat - Input: highest Koc_{SLUDGE}* for partition coefficient in raw sewage (Kp_S) and activated sludge (Kp_{AS})	Not needed

410 * $n_{SLUDGE} \geq 3$: geometric mean, $n_{SLUDGE}=2$: worst case
411 ** $n_{SOIL} \geq 4$: geometric mean, $n_{SOIL} = 3$: worst case
412

413 In order to extract the active substance from sludge or soil, the best available extraction techniques
414 should be used. This means that various extraction methods should be used with increasing strength,
415 e.g. according to the methodology as proposed by ECETOC (2013b). The evaluation of the feasibility of
416 various extraction techniques should be reported in the final study report. Usually, a direct method
417 with radiolabelling provides the most robust information.

418 **Ready biodegradability**

419 The readily biodegradability of a substance should be determined according to OECD 301. The
420 microbial community should not be pre-exposed to the test compound in this test, and addition of
421 more inoculum is not allowed. OECD 301 can be waived if OECD 314 B (for PEC refinement in Phase II
422 Tier B) or OECD 308 (for PBT assessment or PEC refinement for groundwater) is performed. The
423 results of OECD 301 are used for triggering soil and groundwater assessment and in the Simple Treat
424 calculation. Substances classified as not readily biodegradable are considered potentially persistent.

425 ***4.2.1.3. Ecotoxicity studies***

426 To determine the aquatic ecotoxicity, chronic ecotoxicity data i.e. No Observed Effect Concentration
427 (NOEC) or 10% effect concentration (EC10) for species from three trophic levels are required (See
428 **Table 1**). The risk assessment for the aquatic and sediment compartment is based on chronic
429 exposure and effects because the emission of pharmaceutical residues into surface water is continuous.

Studies with other aquatic test species and/or studies providing other endpoints than the standard OECD endpoints (growth, mortality, reproduction)[1] may also be used, provided they are relevant for population dynamics (according to the description in the Water Framework Directive EQS (European Communities, 2011).

The ecotoxicity tests should be performed under the conditions as described in their respective test guidelines. Validity criteria as described in the test guidelines should be reported and if these are not met, the test should be repeated.

Concentrations should be measured analytically and results should be based on measured concentrations when measured concentrations are not within 80-120% of nominal concentrations. When a reliable concentration-response curve is observed, the NOEC as well as the EC10 should be reported. The EC10 is preferred over the NOEC for PNEC derivation, even if the former is higher than the latter.

A limit test, as defined in the respective OECD ecotoxicity guidelines, may be used to determine the correct exposure concentrations. This can only replace a definitive test when no effects are observed at the limit concentration and no risk is identified. If a PNEC is based on an 'unbounded' value, e.g., a higher than- NOEC (NOEC > X mg/L), the RQ (PEC/PNEC) would also become unbounded (PEC/PNEC < XX). If this RQ is ≥ 1, a risk is identified and a concentration-response relationship should always be established using an appropriate concentration range, resulting in a 'bounded' value for the PNEC and a subsequent concrete RQ. Similarly, when several concentrations are tested but no EC10 or NOEC can be determined because there is a significant effect at the lowest test concentration, the test should be repeated with lower test concentrations in order to establish a correct concentration-response relationship.

Regarding the algal test, the use of a green alga is generally recommended for OECD 201. For some compounds, such as antibiotics, the use of cyanobacteria is more appropriate (See section 4.3.1). In both situations, initial growth rate is the preferred endpoint, even if the endpoint biomass (yield) results in lower (no-)effect concentration (see also section R.7.8.4.1. in ECHA, 2017b). The high growth rate of algal cells makes it possible for algal population to recover within the 72 h test duration as a result of a decline in exposure concentration (e.g. through hydrolysis and photolysis). However, recovery should be disregarded, as algae act as a model organism for all aquatic photoautotrophic organisms, including aquatic macrophytes with a much longer generation time.

For endocrine active substances (EAS), the fish early life stage (FELS) test should be replaced by other, more sensitive test(s), see section 4.3.2.

4.2.2. Trigger values for soil, groundwater, and secondary poisoning

For substances entering Phase II risk assessment, the surface water, sediment and STP compartments always require assessment. If the active substance meets certain trigger values, the risk assessment should also be performed for soil, groundwater and/or secondary poisoning. These trigger values are outlined below.

Soil

Active substances with high affinity for organic carbon have a greater likelihood of accumulating in sludge and ending up in the soil, unless the active substance is readily biodegradable. However, substances with lower adsorption affinity may also be present in sludge at high concentrations, when

[1] Behaviour is an example of an ecotoxicological endpoint not yet established as a reliable and standardised endpoint. It may however be very relevant for neuro-active substances and when standardised guidelines become available, be taken up in a tailored risk assessment scheme for neuro-active substances.

the release to sewage treatment plants is high. Hence, the final exposure of soil organisms depends on both main parameters, i.e. the properties of the pharmaceutical (Koc value) and the total release to the wastewater flow, which again depends on the dose and the fraction of a population receiving the active substance during a given time. The PEC_{SW} calculated in Phase I, reflects directly these parameters, as it disregards processes such as biodegradation or retention of the active substance in the STP. Hence, the PEC_{SW} is used in combination with Koc to trigger assessment for the soil compartment, see **Table 3** and section 4.2.6.

Table 3: Combined trigger values for substances entering a risk assessment for soil organisms

Koc_{SLUDGE} * [L kg^{-1}]	**PEC_{SW}** [µg L^{-1}]
$Koc_{SLUDGE} \geq 10{,}000$	Trigger irrespective of PEC_{SW}
$5{,}000 \leq Koc_{SLUDGE} < 10{,}000$	≥ 1
$2{,}500 \leq Koc_{SLUDGE} < 5{,}0000$	≥ 2
$1{,}000 \leq Koc_{SLUDGE} < 2{,}500$	≥ 3
$Koc_{SLUDGE} < 1000$	No trigger – irrespective of PEC_{SW}

* $n_{SLUDGE} \geq 3$: geometric mean, $n_{SLUDGE}=2$: worst case

Groundwater

A risk assessment for groundwater is required when the Koc_{SLUDGE} is ≤ 10,000 L kg^{-1}, unless the substance is readily biodegradable (see section 4.2.6).

Secondary poisoning

A secondary poisoning risk assessment is required if the octanol/water partition coefficient (log Kow) is ≥ 3 (see section 4.2.8).

4.2.3. Surface water

To determine a potential risk to the surface water compartment, the PEC_{SW} (as calculated in Phase I) is compared to the $PNEC_{SW}$. This PNEC is derived using experimental chronic ecotoxicity data for fresh water species (**Table 1**) because continuous exposure of the aquatic environment via effluents from STPs is assumed. When the PEC/PNEC ratio is ≥ 1, a risk to the aquatic compartment as a whole (not a particular sensitive group of species) is indicated. If a risk is identified in Phase II Tier A, a refined assessment may be performed in Phase II Tier B.

4.2.3.1. Phase II Tier A assessment for surface water

Exposure assessment for surface water

The final PEC_{SW} as calculated in Phase I should be used (see Eq. 1-3).

Effect assessment for surface water

To derive a PNEC, chronic ecotoxicity data for species from at least three trophic levels (algae, Daphnia and fish) are required, as described in section 4.2.1.

The $PNEC_{SW}$ is calculated by applying an assessment factor (AF) of 10 to the lowest EC10 or NOEC value from the aquatic test species. The AF is an expression of the degree of uncertainty in the extrapolation from a limited number of test species to complex ecosystems in the actual environment and accounts for, inter-species variations in sensitivity, intra-species variability and laboratory data to field impact extrapolation.

505 **Table 4:** Ecotoxicological studies used in the effect assessment for surface water

Study	Endpoint[a]	Guideline
Aquatic toxicity (4.2.1.3)		
Algae, growth inhibition	EC10 or NOEC [mg L^{-1}]	OECD 201
Daphnia sp. reproduction	EC10 or NOEC [mg L^{-1}]	OECD 211
Fish, Early life stage toxicity	EC10 or NOEC [mg L^{-1}]	OECD 210

506 [a] EC10 values are preferred over NOECs in the risk assessment.
507

508 Risk characterisation

509 Using the $PNEC_{SW}$, the risk quotient (RQ) for the surface water is determined (equation 4).

510

$$RQ_{SW} = \frac{PEC_{SW}}{PNEC_{SW}} \qquad \textbf{Eq. 4}$$

511

512 If the surface water RQ is < 1, then further testing in surface water is not required and it can be
513 concluded that the active substance is unlikely to represent a risk to surface water.

514 If the surface water RQ is ≥1, a Tier B assessment is required.

515 ***4.2.3.2. Phase II Tier B assessment for surface water***

516 When a risk is established in Tier A, the PEC_{SW} may be refined using one or more of the options below:

517 • Fpen, if not refined in Phase I Tier A. For more information, see Q6 in section 4.1.

518 • Consumption data

519 • Metabolism

520 • Potential removal in the STP.

521 Refinement of PEC_{SW} using consumption data

522 At the renewal of a marketing authorisation for a medicinal product, consumption data on the active
523 substance may be used to refine F_{PEN} (equation 5) and the PEC_{SW}, with the possibility of a
524 consequential impact on the conclusion of the previous ERA. The data used should come from a reliable
525 and publicly available source and demonstrate a stable consumption over the last 3 or more years. A
526 market share of 100% is always assumed. If regional differences exist, data from the member state
527 with the highest calculated F_{PEN} should be used.

528

$$F_{PEN-REFINED} = \frac{Consumption}{DOSE_{AS}\ x\ Inhabitants\ x\ 365} \qquad \textbf{Eq. 5}$$

529

Parameters used in Eq. 5:

Parameter	Description	Unit
$F_{PEN\text{-}REFINED}$	Refined fraction of a population receiving the active substance during a given time	[--]
Consumption	Consumption of active substance in geographic region per year	[mg $year^{-1}$]
$DOSE_{AS}$	Maximum daily dose of the active substance consumed per inhabitant	[mg inh^{-1} d^{-1}]
Inhabitants	Number of inhabitants in the region covered by the consumption data.	[inh]

Refinement of PEC_{SW} using metabolism data

If a potential risk for the medicinal product to the environment has been identified based on the total residue approach, then the total residue approach may be abandoned and the risk may be refined by subtracting the fractions of metabolites. If the total residue approach is abandoned, a full Phase II risk assessment is required for each metabolite constituting ≥10% of the administered dose. The PEC is then calculated separately for the parent compound and these metabolites and all resulting PEC/PNEC ratios are summed for the evaluation of environmental risk of the product. If it is not possible to perform the ERA for the metabolites excreted in fractions ≥ 10% of the dose, the total residue approach should be used. If a risk is identified and it is not possible to refine the risk by testing the metabolites, the ERA should be concluded with the statement that the use of the product is expected to result in a risk to the environmental compartment(s) concerned.

The following approach may be used for this refinement:

$$PEC_{SW-REFINED} = \frac{DOSE_{AS} \times F_{PEN} \times F_{EXCRETA}}{WASTEW_{INHAB} \times DILUTION} \qquad \textbf{Eq. 6}$$

Parameters used in Eq. 6:

Parameter	Description	Unit	Default value / reference
$PEC_{SW\text{-}REFINED}$	Predicted environmental concentration in surface water refined in Phase II Tier B	[mg L^{-1}]	-
F_{PEN}	Fraction of a population receiving the active substance during a given time, from Tier A	[--]	See Eq. 1-3
$F_{EXCRETA}$	Fraction of substance excreted	[--]	-
$DOSE_{AS}$	Maximum daily dose of the active substance consumed per inhabitant	[mg inh^{-1} d^{-1}]	-
$WASTEW_{INHAB}$	Amount of wastewater per inhabitant per day	[L $inh^{-1}d^{-1}$]	200
DILUTION	Dilution factor	[--]	10

548 Refinement of PEC_{SW} with STP modelling using the SimpleTreat model

549 Refinement of PEC_{SW} may also be performed by a model simulation using the latest version of
550 SimpleTreat. (Download: https://www.rivm.nl/en/Topics/S/Soil_and_water/SimpleTreat; instruction:
551 https://www.umweltbundesamt.de/publikationen/application-of-simpletreat-40-in-european-
552 substance) by incorporating:

553 • Adsorption of the active substance to sewage sludge in STPs, using the data from the estimation of
554 the adsorption coefficient (OECD 106)

555 • Test for ready biodegradability in the STP (OECD 301)/measured removal rates using the OECD
556 314 B study.

557 **Table 5:** Fate studies used in Phase II Tier B refinement of PEC_{SW}

Study	Endpoint	Guideline
Fate properties (4.2.1.2)		
Adsorption - Desorption Using a Batch Equilibrium Method in sludge and soil	Koc_{SLUDGE} (L kg^{-1}) Koc_{SOIL}, Kd_{SOIL} (L kg^{-1})	OECD 106
Ready Biodegradability Test	Information if readily/not readily biodegradable	OECD 301

558

559 Calculation of emission of active substance per day

560 For local scale assessments, it is assumed that one point source is releasing its wastewater to one STP.
561 The concentration in the influent of the STP, i.e. the untreated wastewater, can be calculated from the
562 local release to wastewater and the influent flow to the STP. The influent flow equals the effluent
563 discharge.

564

$$Elocal_{WATER} = DOSE_{AS} \times F_{EXCRETA} \times F_{PEN} \times CAPACITY_{STP} \qquad \textbf{Eq. 7}$$

565

566 Calculation of the STP influent concentration

567 For local scale assessments, it is assumed that one point source is releasing its wastewater to one STP.
568 The concentration in the influent of the STP, i.e. the untreated wastewater, can be calculated from the
569 local release to wastewater and the influent flow to the STP. The influent flow equals the effluent
570 discharge.

571

$$Clocal_{INF} = \frac{Elocal_{WATER}}{WASTEW_{INHAB} \times CAPACITY_{STP}} \qquad \textbf{Eq. 8}$$

572

573 Calculation of the STP-effluent concentration

574 The concentration of the effluent of the STP is given by the fraction directed to the effluent and the
575 concentration in untreated wastewater as follows:

576

$$Clocal_{EFF} = Clocal_{INF} \times Fstp_{WATER} \qquad \textbf{Eq. 9}$$

The fraction of the active substance discharged to the water phase in STP ($Fstp_{WATER}$) can be modelled with SimpleTreat (current version 4.0). The model is used to estimate chemical emission from STPs and exposure to surface water. The following input parameters are essential:

- Molecular mass, water solubility, vapour pressure (consideration of volatilization)
- **Adsorption** of the active substance to sewage sludge in STPs, the Koc values derived for sludge by the batch equilibrium method (OECD 106) is required. Koc derived from soil or sediment cannot be considered. The lowest Koc derived from sludge should be used (n=2). If 3 or more types of sludge are available (n ≥ 3) the geometric mean can be used.
- Biodegradation in activated sludge as input for Simple Treat can be estimated by three different methods:
  - Method 1: estimated from OECD/EU standardized biodegradability tests according to OECD 301 series, 310 or 302 series (recommended). The aquatic first order degradation constant k biodeg [h^{-1}] should be used.
  - Method 2: active substance is biodegradable in activated sludge batch test according to OECD 314B. The first order degradation constant k biodeg [h^{-1}] valid for combined aqueous phase/sludge should be used.
  - Method 3: active substance is biodegradable in activated sludge simulation test according to OECD 303B. The first order degradation constant k biodeg [h^{-1}] valid for aqueous phase should be used.

No changes of the default values for the operational parameters of the sewage treatment (facility type: municipal) are needed. In the output-sheet the distribution is given for four compartments:

- Air [%]
- Water [%] = $Fstp_{WATER}$ [%], needed for refinement of PEC_{SW}
- Primary settler [%]
- Surplus sludge [%]

$Fstp_{SLUDGE}$ is the sum of primary settler and surplus sludge [%]

Calculation of the refined surface water concentration

The starting point for the calculation is the concentration of the active substance in the STP effluent. Dilution in the receiving surface water and adsorption to suspended matter are then considered.

The partition coefficient between suspended matter and water, Kp_{SUSP}, may be estimated from the Koc of the active substance, determined for soil by taking into account different organic carbon contents of the media. The lowest Koc derived from soil should be used. If 4 or more soils are available the geometric mean may be used. If Kd/Kf does not correlate with oc, the Kf/Kd –value should be used as Kp_{SUSP}.

$$Kp_{SUSP} = Foc_{SUSP} \times Koc_{\mathrm{SOIL}} \qquad \textbf{Eq. 10}$$

$$FACTOR = 1 + Kp_{SUSP} \times SUSP_{WATER} \qquad \textbf{Eq. 11}$$

614

$$PEC_{SW-REFINED} = \frac{Clocal_{EFF}}{DILUTION \times FACTOR} \qquad \textbf{Eq. 12}$$

615

616 Parameters used in Eq. 7-12:

Parameter	Description	Unit	Default value / reference
$Elocal_{WATER}$	Local release rate to influent wastewater during episode	[kg d^{-1}]	-
$DOSE_{AS}$	Maximum daily dose of the active substance consumed per inhabitant	[mg inh^{-1} d^{-1}]	-
$F_{EXCRETA}$*	Fraction of active substance excreted	[--]	-
F_{PEN}	Fraction of a population receiving the active substance during a given time	[--]	See Eq. 1-3
$CAPACITY_{STP}$	Capacity of the STP (inhabitants)	[inh]	10,000
$Clocal_{INF}$	Concentration in untreated wastewater	[mg L^{-1}]	-
$WASTEW_{INHAB}$	Amount of wastewater per inhabitant per day	[L $inh^{-1}d^{-1}$]	200
$Clocal_{EFF}$	Concentration of active substance in the STP effluent	[mg L^{-1}]	-
$Fstp_{WATER}$	Fraction of release directed to water by STP	[--]	See output sheet of SimpleTreat
Kp_{SUSP}	Solids/water partition coefficient for suspended matter	[L kg^{-1}]	-
Foc_{SUSP}	Fraction of organic carbon in suspended matter	[--]	0.1
Koc_{SOIL}	Partition coefficient between organic carbon and water derived from soil	[L kg^{-1}]	See Table 2
FACTOR	Factor taking the adsorption to suspended matter into account	[--]	-
$SUSP_{WATER}$	Concentration of suspended matter (dry weight)	[mg L^{-1}]	15
$PEC_{SW\text{-}REFINED}$	Predicted environmental concentration in surface water refined in Phase II Tier B	[mg L^{-1}]	-
DILUTION	Dilution factor	[--]	10

617 *This should include unchanged active substance and the fractions of dose excreted as metabolites unless the total residue approach
618 is abandoned

619

620 Risk characterisation

621 The risk quotient (RQ) for the surface water is determined using the $PNEC_{SW}$ (equation 13).

622

$$RQ_{SW} = \frac{PEC_{SW-REFINED}}{PNEC_{SW}} \qquad \textbf{Eq. 13}$$

623

If the RQ for surface water is < 1, it may be anticipated that the active substance in the medicinal product will not pose a risk to the aquatic environment.

When a risk to the surface water ecosystem cannot be excluded, the applicant should propose adequate precautionary and safety measures to protect surface water ecosystems (see also section 7).

4.2.4. Sediment

For the sediment risk assessment, PEC_{SED} is derived from PEC_{SW} as calculated in phase I (see equation 1-3) using equilibrium partitioning (EqP) between water and sediment consisting of freshly deposited suspended matter. A $PNEC_{SED}$ is derived using tests with sediment dwelling organisms. Both PEC and PNEC should be based on sediment with equal (normalized) organic carbon content and on a dry weight basis.

4.2.4.1. Phase II Tier A assessment for sediment

Exposure assessment for sediment

Koc should be determined for a minimum of three soils (see section 4.2.1.2). If four or more Koc values are available, then the geometric mean should be used. Otherwise, the highest Koc should be used. If the adsorption to soil does not correlate with the organic carbon the solid-water partitioning coefficient should be used as Kp_{SUSP} (highest Kd = Kp_{SUSP}).

Table 6: Fate study used in Phase II Tier A PEC_{SED} calculation

Study	Endpoint	Guideline
Fate properties (4.2.1.2)		
Adsorption - Desorption Using a Batch Equilibrium Method in soil	Koc_{SOIL}, Kd_{SOIL} [L kg^{-1}]	OECD 106

The concentration of the active substance in sediment is calculated according to equation 14.

$$PEC_{SED} = \frac{K_{SUSP-WATER}}{RHO_{SUSP}} \times PEC_{SW} \times 1000 \qquad \textbf{Eq. 14}$$

The partitioning coefficient between suspended matter and water is calculated according to equation 15.

$$K_{SUSP-WATER} = Fwater_{SUSP} + (Fsolid_{SUSP} \times Kp_{SUSP} \times RHO_{SOLID} \times 10^{-3}) \qquad \textbf{Eq. 15}$$

If the adsorption to soil does not correlate with the organic carbon the solid-water partitioning coefficient should be used as Kp_{SUSP} (highest Kd = Kp_{SUSP}).

$$Kp_{SUSP} = Foc_{SUSP} \times Koc_{SOIL} \qquad \textbf{Eq. 16}$$

654

655 Parameters used in Eq. 14-16:

Parameter	Description	Unit	Default value
PEC_{SED}	Predicted environmental concentration in sediment related to wet weight	[mg kg^{-1} w.w]	-
$K_{SUSP\text{-}WATER}$	Partitioning coefficient between suspended matter and water	[--]	See Eq. 15
RHO_{SUSP}	Density of suspended matter	[kg m^{-3}]	1,150
PEC_{SW}	Predicted environmental concentration in surface water calculated in Phase I	[mg L^{-1}]	See Eq. 1-3
$Fwater_{SUSP}$	Fraction of water in suspended matter	[--]	0.9
$Fsolid_{SUSP}$	Fraction of solids in suspended matter	[--]	0.1
Kp_{SUSP}	Solids/water partition coefficient for suspended matter	[L kg^{-1}]	See Eq.16
RHO_{SOLID}	Density of the solid phase	[kg m^{-3}]	2,500
Foc_{SUSP}	Weight fraction of organic carbon in suspended solids	[kg kg^{-1}]	0.1
Koc_{SOIL}	Partition coefficient between organic carbon and water derived from soil	[L kg^{-1}]	See Table 2. Determined using OECD 106

656

657 PEC_{SED} is related to **wet** sediment, which is expressed as freshly deposited suspended solid matter with
658 an organic carbon content of 10%. The PEC_{SED} based on dry weight is obtained by equation 17.

659

$$PEC_{SED\_DW} = PEC_{SED} \times CONV_{SUSP}$$

660

$$PEC_{SED\_DW} = \frac{PEC_{SED}\ x\ RHO_{SUSP}}{Fsolid_{SUSP} \times RHO_{SOLID}} \qquad \textbf{Eq. 17}$$

661

$$PEC_{SED\_DW} = PEC_{SED} \times 4.6$$

662

663 Parameters used in Eq. 17:

Parameter	Description	Unit	Default value / reference
PEC_{SED_DW}	Predicted environmental concentration in sediment related to dry weight	[mg kg^{-1} d.w.]	-
PEC_{SED}	Predicted environmental concentration in sediment related to wet weight	[mg kg^{-1} w.w.]	See Eq. 13
$CONV_{SUSP}$	Conversion factor	[kg_{WW} kg_{DW}^{-1}]	4.6
RHO_{SUSP}	Bulk density of (wet) suspended matter	[kg m^{-3}]	1,150
$Fsolid_{SUSP}$	Fraction of solids in suspended matter	[--]	0.1
RHO_{SOLID}	Density of the solid phase	[kg m^{-3}]	2,500

664

The fraction bound residue that may have been determined in fate studies, may not be subtracted from the PEC_{SED}.

Effect assessment for sediment

To determine a $PNEC_{SED}$, a minimum of one study with sediment dwelling organisms should be performed using a sediment-water test system (**Table 7**). In general, tests using a spiked sediment procedure are preferred. However, if the characteristics of the test substance make it impossible to spike sediment in a reliable manner (e.g. high water solubility, low binding affinity to sediment) it may be more appropriate to use the spiked water procedure.

For ionisable compounds, care should be taken that testing is performed at an environmentally relevant pH (5-9). For these compounds, a tailor-made approach may be followed if it can be substantiated and is well reported.

Table 7: Ecotoxicological standard tests with benthic species useful for the effect assessment in sediment

Study	Endpoint[a]	Guideline
Chironomid, spiked water/sediment	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 218/219
Chironomid, life-cycle study	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 233
Lumbriculus sp., sediment-water toxicity	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 225

[a] EC10 values are preferred over NOECs in the risk assessment.

If data from a single chronic sediment test is available, an assessment factor of 100 should be applied to the EC10 or NOEC in order to derive the PNEC. If two long-term tests with species representing different living and feeding conditions are available, an assessment factor of 50 may be applied to the lowest EC10 or NOEC to obtain the $PNEC_{SED}$.

Results from sediment toxicity tests should be recalculated into a standard sediment with an organic carbon content of 10% (fraction of 0.1) according to Eq. 18.

$$EC10\ or\ NOEC_{ST\ SED} = EC10\ or\ NOEC_{TEST\ SED} \times \frac{Foc_{ST\ SED}}{Foc_{TEST\ SED}} \qquad \textbf{Eq. 18}$$

Parameters used in Eq. 18:

Parameter	Description	Unit	Default value
$Foc_{ST\ SED}$	Fraction of organic carbon in standard sediment	[--]	0.1
$Foc_{TEST\ SED}$	Fraction of organic carbon in test sediment	[--]	-

Risk characterization

Using PEC_{SED} and $PNEC_{SED}$, the RQ for the sediment compartment is determined using equation 19.

$$RQ_{SED} = \frac{PEC_{SED}}{PNEC_{SED}} \qquad \textbf{Eq. 19.}$$

If the risk quotient is ≥ 1, risk refinement may be performed in Phase II - Tier B.

4.2.4.2. Phase II Tier B assessment for sediment

If a risk is identified in Tier A, refinement of PEC_{SW} (see section 4.2.3.2) may also be used for Tier B sediment assessment. If a risk to sediment organisms still cannot be excluded, the applicant should propose adequate precautionary and safety measures to protect sediment ecosystems (see also section 7).

4.2.5. Sewage Treatment Plant

The functioning of STPs is essential for good water quality management. Substances with anti-microbial activity may affect microbial communities. The microbial community most likely exposed to the highest concentrations of the substance(s) is the activated sludge community. In order to evaluate the anti-microbial effects of anti-microbial substances, the activated sludge respiration inhibition test (OECD 209) should be used.

4.2.5.1. Phase II Tier A assessment for STP

Exposure assessment for STPs

To determine the risk for STPs, PEC_{SW} as calculated in phase I (see Eq. 1-3) should be recalculated into a PEC_{STP}. This is achieved by multiplying the PEC_{SW} with a factor of 10, as there is no dilution of effluent with surface water.

Effect assessment for STP

The PNEC is based on the respiration inhibition test for activated sludge (OECD 209), by applying an assessment factor of 10 to the EC10 or NOEC value.

Table 8: Ecotoxicological study used in the effect assessment for STP

Study	**Endpoint**[a]	**Guideline**
Functioning of STP		
Activated sludge, respiration inhibition	EC10 or NOEC [mg L^{-1}]	OECD 209

[a] EC10 values are preferred over NOECs in the risk assessment.

Risk characterisation

Using the $PNEC_{MICROORGANISMS}$, the risk quotient (RQ) for the STP is determined (equation 20).

$$RQ_{MICROORGANISMS} = \frac{PEC_{STP}}{PNEC_{MICROORGANISMS}} \qquad \textbf{Eq. 20}$$

When the risk quotient is ≥ 1, risk refinement options as described for surface water may be used in Phase II Tier B.

4.2.5.2. Phase II Tier B assessment for STP

The exposure concentration in the aeration tank of the SimpleTreat model ($PEC_{AERATION\ TANK}$) should be used to refine the risk quotient for microorganisms. $PEC_{AERATION\ TANK}$ is equal to $Clocal_{EFF}$, see also Eq. 9 in *4.2.3.2.*

Explanation of Parameters:

Parameter	Description	Unit	Default value / Reference
PEC_{STP}	Predicted environmental concentration in the STP effluent	[mg L^{-1}]	-
$PEC_{AERATION\ TANK}$	Predicted environmental concentration in the aeration tank of the sewage treatment plant.	[mg L^{-1}]	Equal to $Clocal_{EFF}$ (see Eq. 7)

4.2.6. Groundwater

Entry into the groundwater is considered to be via bank filtration, except for substances with an average Koc >10,000 L kg^{-1} or for substances that are readily biodegradable. It is assumed that the exposure of groundwater via sewage sludge incorporated into soil can be disregarded with reference to the high sorption affinity of these active substances to the soil.

4.2.6.1. Phase II Tier A assessment for groundwater

Exposure assessment for groundwater

The groundwater PEC (PEC_{GW}) is based on the PEC_{SW} as calculated in phase I (see eq. 1-3) and is estimated by a simple equation.

$$PEC_{GW} = 0.25 \times PEC_{SW} \qquad \textbf{Eq. 21}$$

Effect assessment for groundwater

The $PNEC_{GW}$ is based on the $PNEC_{SW}$ (see 4.2.3.1) and an additional assessment factor. Groundwater ecosystems are fundamentally different to surface water ecosystems and therefore may be more vulnerable as they lack the ability to recover from perturbations. Consequently, an additional assessment factor of 10 should be applied to extrapolate the $PNEC_{GW}$ from the $PNEC_{SW}$ (Eq. 22 below).

$$PNEC_{GW} = \frac{PNEC_{SW}}{10} \qquad \textbf{Eq. 22}$$

Risk characterization

The risk quotient (RQ) for the groundwater compartment is determined using the PNEC for groundwater (equation 23).

$$RQ_{GW} = \frac{PEC_{GW}}{PNEC_{GW}} \qquad \textbf{Eq. 23}$$

If the risk quotient is ≥ 1, risk refinement options should be used in Phase II Tier B as described below.

4.2.6.2. Phase II Tier B assessment for groundwater

If the RQ_{GW} is ≥1, further evaluation is needed in Tier B using one or more of the options below.

- Calculate the PEC_{SW}, refined as described in chapter 4.2.3.2.
- Groundwater modelling for a realistic worst case scenario according to SiMBaFi – a bank filtration simulation model. The model and a detailed description can be downloaded here: www.uba.de/simbafi

The following parameters are needed:

- $PEC_{SW\text{-}REFINED}$ as described in section 4.2.3.2.
- Adsorption of the active substance to soil derived from batch equilibrium test (OECD 106). SiMBaFi requires the non -oc-normalized Kd or Kf – value (Kf - Freundlich adsorption coefficient) as input. The lowest Kd/Kf derived from soil should be used (n=3). If 4 or more soils are available the geometric mean may be used. Kd derived from sludge cannot be used.
- Degradation as DT 50 value derived from an OECD 308 study (total system, calculated using single first order kinetics, normalised to 12°C, highest value of 2 test systems).

Table 9: Fate studies used for groundwater risk assessment

Study	Endpoint	Guideline
Fate properties (4.2.1.2)		
Adsorption - Desorption Using a Batch Equilibrium Method in soil	Kd_{SOIL}/Kf_{SOIL} [L kg^{-1}]	OECD 106
Aerobic Transformation in Aquatic Sediment Systems	DT50 value (total system, SFO, 12°C normalisation, highest value of 2 test systems)	OECD 308

For the calculation of the PEC_{GW} the "realistic worst case" determined in SiMBaFi should be used, i.e. a groundwater flow time of 5 days between the surface water and the groundwater well. For calculation four steps are needed as described below:

Calculation of retardation:

$$Rf = 1 + \left(\frac{1-n}{n}\right) \times \rho s \times Kd_{SOIL} \qquad \textbf{Eq. 24}$$

Calculation of flow time for the active substance

SiMBaFi combines the calculation of active substance transport velocity and transport time for the active substance for the distance between bank line and production well to the following equation (eq. 25):

$$t_{AS} = t_{GW} \times Rf \qquad \textbf{Eq. 25}$$

Calculation of concentration at production well

This step considers elimination by biological degradation of the active substance during their transport from the surface water to the production well with an exponential equation (eq. 26):

$$PEC_{PRODUCTION\ WELL} = PEC_{SW-REFINED} \times e^{\left(\frac{-ln2}{DT_{50}} \times t_{as}\right)} \qquad \textbf{Eq. 26}$$

As the percentage of bank filtrate at the production well is assumed to be 100 % the resulting PEC_{GW} equals the calculated concentration in the production well (eq. 27).

$$PEC_{GW-REFINED} = PEC_{PRODUCTION\ WELL} \qquad \textbf{Eq. 27}$$

Parameters used in Eq. 24-27:

Parameter	**Description**	**Unit**	**Default value / Reference**
Rf	Retardation factor	[--]	-
n	Porosity – the default value is typical for an aquifer composed of sand and gravel	[--]	0.35
ρs	Solid density – the default value representing characteristic density for quartz as the main component of porous aquifer systems.	[g cm^{-3}]	2.65
Kd_{SOIL} / Kf_{SOIL}	Adsorption coefficient (not oc normalized)	[L kg^{-1}]	See Table 2. Determined using OECD 106
t_{AS}	Flow time of the active substance	[d]	-
t_{GW}	Groundwater flow time - the default value representing a realistic worst case for flow time between surface water and well	[d]	5
$PEC_{PRODUCTION\ WELL}$	Predicted environmental concentration at production well	[mg L^{-1}]	-
$PEC_{SW\text{-}REFINED}$	Predicted environmental concentration in surface water, refined in Phase II Tier B	[mg L^{-1}]	See 4.2.3.2
DT50	Half-life for biological transformation, water/sediment total system:	[d]	-
$PEC_{GW\text{-}REFINED}$	Predicted environmental concentration in the groundwater after entry by bank filtration, refined in Phase II Tier B	[mg L^{-1}]	-

Risk characterisation

The refined RQ_{GW} should be recalculated using the refined PEC_{GW} and the PNEC value from Phase II Tier A.

When a risk to the groundwater ecosystem cannot be excluded, the applicant should propose adequate precautionary and safety measures to protect groundwater ecosystems (see section 7).

4.2.7. Soil

A combined trigger for the soil compartment (see 4.2.2 and **Table 3**) aims to ensure a soil assessment for substances with high release to the sewage treatment plants, even if the adsorption is lower than a Koc value of 10 000 L kg^{-1} indicates.

To determine a possible risk to the soil compartment, the PEC_{SOIL} is compared to the $PNEC_{SOIL}$. This $PNEC_{SOIL}$ is derived using experimental long-term ecotoxicity data for soil microorganisms, soil dwelling invertebrates and plant species (**Table 11**). Since sludge associated active pharmaceutical residues may be available in soil compartment for a long time, short-term effect tests are inappropriate for risk assessment. When the PEC/PNEC ratio is ≥ 1, a risk to the entire soil compartment (not a particular sensitive group of species) is indicated. If a risk is identified in Phase II Tier A, a refined assessment may be performed in Phase II Tier B.

4.2.7.1. Phase II Tier A assessment for soil

Tier A Exposure assessment for soil

The Tier A exposure assessment considers sludge application as the major entry path for the active substance to be released to the soil environment. In a first step, the initial concentration in soil after the first application is calculated using the predicted concentration of the active substance in sludge. For substances which accumulate and are not easily degraded, the concentration in soil after repeated sludge application should also be assessed. In order to consider the biodegradation of the active substance in soil in between sludge applications a study on degradation in soil (OECD 307) is required.

Table 10: Fate studies used in Phase II Tier A exposure assessment for soil

Study	Endpoint	Guideline
Adsorption - desorption using a Batch Equilibrium Method in sludge	Koc_{SLUDGE} [L kg^{-1}]	OECD 106
Degradation in soil*	DT50 [d]	OECD 307

** In case three soils or more were tested in OECD 307, using the geometric mean DT50 value is appropriate. In case of fewer soils were tested the highest value should be used as DT50 in the calculation. Studies must reflect environmental temperatures in Europe and therefore preferably be conducted at 12°C or extrapolation of degradation half-lives to 12°C should be considered. See section 5.2.2.1 for more information.*

Concentration in soil after the first sludge application

The initial concentration of the active substance in soil (PEC_{SOIL}) after the first sludge application (t=0) is shown in Equation 28. The default mixing depth and sludge application rates are in compliance with the procedure in the ECHA Environmental Assessment (R16) (EU, 2016).

$$PEC_{SOIL} = \frac{C_{SLUDGE} \times Appl_{SLUDGE}}{Depth \times Density} \qquad \textbf{Eq. 28}$$

The concentration in sewage sludge (C_{sludge}) is calculated using equation 29.

$$C_{SLUDGE} = \frac{Fstp_{SLUDGE} \times Elocal_{WATER}}{Sludgerate} x\ 1000000 \qquad \textbf{Eq. 29}$$

Parameters used in Eq. 28-29:

Parameter	Description	Unit	Default value / Reference
PEC_{SOIL}	Predicted environmental concentration in soil after the first application	[mg kg^{-1} w.w.]	-
C_{SLUDGE}	Concentration in sludge	[mg kg^{-1} w.w.]	-
$Appl_{SLUDGE}$	Yearly sludge application rate	[kg m^{-2}]	0.5
Depth	Mixing depth	[m]	0.2
Density	Bulk density of wet soil	[kg m^{-3}]	1,700
$Fstp_{SLUDGE}$	Fraction found in sludge	[--]	Calculated by SimpleTreat using Koc_{SLUDGE}, see also Table 2
$Elocal_{WATER}$	Local release rate to influent wastewater during episode	[kg d^{-1}]	See Eq. 7, with $F_{EXCRETA}$ = 1
Sludgerate	Rate of sewage sludge production	[kg d^{-1}]	710*

**Default value taken from the ECHA Exposure Assessment Guideline (R16) (EU, 2016).*

The emission rate to influent wastewater ($Elocal_{WATER}$) of the active substance is estimated by Eq. 7 using a default value of 1 for $F_{EXCRETA.}$

Long-term accumulation in soil

If the active substance is not easily degraded, it may accumulate in soil over time resulting from repeated sludge application. It will continue to accumulate until a steady state level is reached. The number of years to reach steady state depends on the half-life of the substance. The concentration in the steady-state year can be calculated by equation 30.

$$PEC_{SOIL(SS)} = \frac{PEC_{SOIL}}{1 - Facc} \qquad \textbf{Eq. 30}$$

The fraction accumulating after one year is calculated by Eq 31.

$$Facc = e^{-365 \times k} \qquad \textbf{Eq. 31}$$

The first rate removal rate can be calculated if the removal rates for degradation, leaching and volatilisation are known, i.e. $k = k_{VOLAT} + k_{LEACH} + k_{BIODEGRADATION}$.

However, removal by volatilisation and leaching ($k_{VOLAT} + k_{LEACH}$) may be disregarded assuming that biodegradation is the main removal constant. Otherwise, guidance for calculating $k_{VOLAT} + k_{LEACH}$ may

849 be found in ECHA Exposure Assessment (Equations R16-47 and R16-48) (ECHA, 2016). The removal
850 by biodegradation is calculated by Eq. 32.

851

$$k_{BIODEGRADATION} = \frac{ln2}{DT50} \qquad \textbf{Eq. 32}$$

852

853 Parameters used in Eq. 30-32:

Parameter	Description	Unit	Default value
$PEC_{SOIL(SS)}$	Predicted environmental concentration in soil in a steady-state situation	[mg kg^{-1} w.w.]	-
PEC_{SOIL}	Predicted environmental concentration in soil after the first application	[mg kg^{-1} w.w.]	See Eq.28
Facc	Fraction accumulating in soil over one year	[--]	-
k	First rate removal (dissipation) rate from soil	[d^{-1}]	-
DT50	Half-life for biodegradation in soil	[d]	-

854

855 PEC_{SOIL} is related to **wet** soil. The PEC_{SOIL} based on dry weight is obtained by equation 33.

856

$$PEC_{SOIL\_DW} = PEC_{SOIL} \times CONV_{SOIL} =$$

857

$$PEC_{SOIL\_DW} = \frac{PEC_{SOIL}\ x\ RHO_{SOIL}}{Fsolid_{Soil} \times RHO_{SOLID}} = \qquad \textbf{Eq. 33}$$

858

$$PEC_{SOIL\_DW} = PEC_{SOIL} \times 1.13$$

859

860 Parameters used in Eq. 33:

Parameter	Description	Unit	Default value / reference
PEC_{SOIL_DW}	Predicted environmental concentration in soil related to dry weight	[mg kg^{-1} d.w.]	
PEC_{SOIL}	Predicted environmental concentration in soil related to wet weight	[mg kg^{-1} w.w.]	See Eq. 28 and 30
$CONV_{SOIL}$	Conversion factor	[kg_{WW} kg_{DW}^{-1}]	
RHO_{SOIL}	Bulk density of wet soil	[kg m^{-3}]	1,700
$Fsolid_{SOIL}$	Fraction of solids in soil	[--]	0.6
RHO_{SOLID}	Density of the solid phase	[kg m^{-3}]	2,500

861

862 **Tier A Effect Assessment for soil**

863 Four tests on different trophic levels are required for the soil compartment, including a functional test
864 with soil microorganisms and ecotoxicological tests with soil dwelling invertebrates and plant species

(***Table 11***). The long-term toxicity to soil organisms should be assessed as active substances in soils may persist for a long time, or accumulation of the substance may occur when sludge is applied over consecutive years. The $PNEC_{soil}$ is calculated by applying an assessment factor (AF) of 10 to the lowest EC10 or NOEC value from the soil test species.

Table 11: Ecotoxicological studies used in the risk assessment for soil organisms

Study	Toxicity endpoint[a]	Guideline
Nitrogen Transformation (28 days)*	< 25% of control**	OECD 216
Terrestrial plants***	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 208
Earthworm / Enchytraeid	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 222/OECD
Collembola	EC10 or NOEC [mg kg^{-1} dry weight]	OECD 232

* Studies should be conducted at 1X and 10X the maximum PEC.
** An assessment factor is not relevant to this endpoint – when the difference in rates of nitrate formation between the lower treatment (i.e. the maximum PEC) and control is equal to or less than 25% at any sampling time before day 28, the active ingredient can be evaluated as having no long-term influence on nitrogen transformation in soils.
***Six plant species from six different families should be tested. It is highly recommended to use species belonging to six different families of four dicotyledonous (including a Brassica species) and two monocotyledonous species, which represent the types of plants grown on agricultural land, which would receive a sludge application.
[a] EC10 values are preferred over NOECs in the risk assessment.

Risk characterisation

Using the appropriate PEC_{SOIL} and the $PNEC_{SOIL}$, the RQ for the soil compartment is determined by equation 34.

$$RQ_{SOIL} = \frac{PEC_{SOIL}}{PNEC_{SOIL}} \qquad \textbf{Eq. 34.}$$

If the risk quotient is ≥ 1, the risk assessment proceeds to Phase II – Tier B.

4.2.7.2. Phase II Tier B Assessment for soil

Tier B Exposure assessment for soil

If a risk for soil organisms has been identified in Tier A, it is possible to refine the emission rate to influent wastewater by using consumption data and metabolism data as performed in Tier B for surface water (see 4.2.3.2).

The refined emission rate to influent wastewater is used to recalculate the sludge concentration C_{SLUDGE} and the relevant PEC_{SOIL}, as described above for Tier A.

Tier B Effect Assessment for soil

If the RQ_{SOIL} from nitrogen transformation in Tier A is still ≥1, further evaluation of the PNEC may be possible in Tier B by extending the microorganisms Nitrogen Transformation Test (OECD 216) to 100 days (**Table 12**).

Table 12: Effect studies used for Tier B assessment for soil organisms

Study	Endpoint	AF	Guideline
Nitrogen Transformation (100 days – extension of Tier A study)	≤ 25% of control	*	OECD 216

* An assessment factor is not relevant to this endpoint – when the difference in rates of nitrate formation between the lower treatment (i.e., the maximum PEC) and control is ≤ 25% at any sampling time before day 100, the substance can be evaluated as having no long-term influence on nitrogen transformation in soils.

Risk characterisation

The refined RQ_{SOIL} should be recalculated using the refined PEC_{SOIL} and the refined PNEC value if applicable. If a risk to the soil ecosystem cannot be excluded at this stage, the applicant should propose adequate precautionary and safety measures to protect soil ecosystems (see also section 7).

4.2.8. Secondary poisoning

Secondary poisoning is a toxic effect on birds and mammals resulting from consumption of contaminated prey (fish or other aquatic organisms). It is relevant for compounds that accumulate through the food chain, mainly lipophilic compounds. Thus, when log Kow is ≥ 3, the potential for secondary poisoning should be evaluated. First, a bioconcentration factor in fish (BCF_{FISH}) should be determined experimentally (**Table 13**). It should be noted that a lack of accumulation in mammals does not exclude a potential for accumulation in fish and other aquatic species. Accumulation may occur as a result of decreased activity of enzymes involved in the transformation of xenobiotics in fish and/or lower trophic levels, differences in exposure routes (e.g. air via lungs vs. water via gills), differences in metabolism, different excretion routes, etc.

When the BCF_{FISH} is > 100 L kg^{-1}, the potential for secondary poisoning should be further assessed using a calculation method. The BCF_{FISH}, together with mammalian toxicity data from the non-clinical safety assessment of the active substance are used to derive a $PNEC_{BIOTA}$. No further experimental work in mammalian species is requested. When mammalian toxicity data are not available further assessment (i.e. calculation of a $PNEC_{BIOTA}$) can be waived.

When BCF_{FISH} is > 2000, the B-criterion according to **Table 16** (PBT assessment) is fulfilled. In this case, it should also be checked whether the T-criterion (**Table 16**) is fulfilled. In this case, the P-criteria (**Table 16**) should be also assessed, either by using the study on degradation in soil (if soil assessment was triggered) or by performing an aquatic degradation study (OECD 308 or 309). In case of a BCF-value > 5000, degradation should be assessed using the vP criteria (**Table 16**).

Bioconcentration factor

The BCF is determined in fish using the OECD 305 test guideline (these results may also be used for the PBT assessment, see section 5.2). Aqueous exposure is the preferred methodology when technically feasible because dietary exposure yields a biomagnification factor (BMF) rather than a BCF, which then should be estimated from the depuration rate constant. The kinetic calculation of BCF (based on uptake and elimination rates and taking dilution due to fish growth into account) is preferred over the steady state calculation (based on concentrations in fish and water) and BCF values should be normalized to 5% lipid content. A minimized study design is also described in OECD 305 but this may only be used for screening purposes. It may not be used to determine an accurate BCF value because it cannot be determined whether steady state is reached (see OECD guidance document No. 264, 2017 for additional information).

Table 13: Trigger for secondary poisoning assessment

Study	Endpoint	Guideline	Trigger for further assessment of secondary poisoning
Bioaccumulation in fish	BCF_{FISH} [L kg^{-1}]	OECD 305	100

Input values

Inputs for the calculation of secondary poisoning potential are the BCF_{FISH} and the most relevant mammalian toxicity data from the non-clinical part of the dossier, i.e. preferably the lowest no observed adverse effect level (NOAEL) from a chronic repeat-dose toxicity study (minimum of 28 days) in the most sensitive species. This NOAEL is converted to a no-effect-concentration in food, (NOEC). This NOEC may be normalised to the caloric content in food according to the Water Framework Directive EQS (European Communities, 2018), and is then used to derive a $PNEC_{BIOTA}$. When only acute studies are available an additional assessment factor is applied to the derivation of the $PNEC_{BIOTA}$ (see ECHA, 2017c; European Communities, 2011) for guidance).

Calculation of secondary poisoning potential

$PNEC_{BIOTA}$ may be converted into a $PNEC_{SW,\ SECPOIS}$ by dividing it by the BCF_{FISH} and BMF. Using this approach, when the $PNEC_{SW,\ SECPOIS}$ is higher than the PEC_{SW}, a risk due to secondary poisoning is identified.

Alternatively, the risk of secondary poisoning for predators in the aquatic food chain may be calculated as the ratio of the concentration of the contaminant in the predator's food (PEC_{BIOTA}) and the no-effect-concentration for the oral intake ($PNEC_{BIOTA}$). If this risk quotient is ≥1, a risk of secondary poisoning is identified. PEC_{BIOTA} is then derived from PEC_{SW} multiplied by BCF_{FISH} (experimental data) and BMF (default value). The BMF is defined as the relative concentration in a predator compared to the concentration in its prey ($C_{PREDATOR}/C_{PREY}$). The default BMF value is based on the experimental BCF_{FISH} and derived according to (ECHA, 2017c, ECHA, 2016 and Water Framework Directive EQS (European Communities, 2011)).

4.3. Tailored assessment for active substances with a specific mode of action

For certain groups of active substances, a tailored assessment is required for the aquatic compartment due to their specific mode of action. This concerns compounds for which the action limit does not apply, such as endocrine active substances (see section 4.3.2), but may also concern compounds for which the action limit applies, such as antibiotics (see section 4.3.1).

For all active substances that require a tailored risk assessment, an ERA Phase II assessment is required for all compartments, including fate aspects. For the aquatic compartment, OECD ecotoxicity tests are available for a number of species that may replace standard test species, depending on the mode of action. For soil and sediment, tailoring with regard to the choice of test species is often not possible.

4.3.1. Antibiotics

For active substances with an antibacterial mode of action, and no other known pharmacological targets, a targeted effect assessment should be performed for the aquatic compartment. Scientific knowledge and empirical data demonstrate that a tailored risk assessment focused on the effects on

lower trophic levels including bacteria, algae and aquatic invertebrates is sufficiently sensitive for antibacterials and fish tests are not required.

Table 14 lists the required studies for active substances with an antibacterial mode of action in Tier A.

Table 14: Required tests in the tailored Tier A assessment for active substances with an antibacterial mode of action

Test	Test species[§]	Endpoint[*]
OECD 201	*Anabaena flos-aquae* (Cyanobacteria)	EC10 or NOEC
OECD 201	*Synechococcus leopoliensis* (Cyanobacteria)	EC10 or NOEC
OECD 201	*Raphidocelis subcapitata* [#](Green algae)	EC10 or NOEC
OECD 211	*Daphnia magna* (Invertebrate)	EC10 or NOEC

[§] The test species recommended in the OECD 201 may be replaced by other species within the same taxonomic group provided it is scientifically and practically justified

[*]For the OECD 201 test, the average specific growth rate is the relevant endpoint to use. The culture should be in exponential growth during all time intervals of the experiment. For the OECD 211, various endpoints (e.g., related to survival or reproduction) are relevant. For both tests: The EC10 value is preferred over the NOEC value if a reliable dose/response curve is generated with concentrations around the EC10 and is hence used for the PNEC derivation when both are available.

 # Raphidocelis subcapitata formerly known as *Pseudokirchneriella subcapitata*

4.3.2. Endocrine active substances (EAS)

Some drug substances may affect the reproduction or development of vertebrate or lower animals at concentrations < 0.01 µg/L. Many studies on the endocrine system published in the peer-reviewed literature document that endogenous hormones can act in vivo at concentrations as low as pg/L. Changes of developmental and reproductive parameters can be major drivers of alterations in population growth. EAS particularly affect developmental and reproductive properties and effects on these parameters are of particular relevance when assessing environmental risk.

Identification of EAS

If there is evidence that the active substance can exert an effect on development or reproduction by directly interacting or interfering with receptors, hormone levels or activities of oestrogens, androgens or other steroid hormones, that active substance should be assessed in Phase II regardless of the predicted environmental concentration. A tailored risk assessment that addresses its specific mechanism of action should be used.

An active substance whose intended pharmacological action targets the endocrine system as described above is considered to be an EAS and should be assessed in Phase II using a tailored risk assessment.

For other active substances, information on potential non-intended endocrine activity should be obtained from the respective part of the dossier. This includes both in vitro and in vivo information. Endocrine-related effects relevant for identification of an EAS include agonism, antagonism and modulation of steroid receptors, steroid hormone levels and changes in steroidogenic tissues (adrenals and gonads), steroidogenic enzyme inhibition and direct interaction with the hypothalamic–pituitary–gonadal axis. The following information should be evaluated using a weight of evidence approach to decide if the substance should be considered to be an EAS and assessed in Phase II using a tailored risk assessment:

In vitro data

- EC50/IC50 in agonist or antagonist mode at levels < 1µM at steroid hormone receptors
- IC50 at levels below 1µM for inhibition of steroidogenic enzymes

In vivo data

- Endocrine-related adverse effects at the lowest observed adverse effect level (LOAEL) in pivotal toxicology, carcinogenicity or reproductive toxicology studies

Changes in steroid hormone levels and changes in steroidogenic tissues (adrenals and gonads) in mammals are considered to be relevant effects. Other relevant effects can include decreases in sperm function and reproductive capability, premature or delayed puberty, changes in oestrous cycles, carcinogenicity in endocrine organs and mammary glands and changes in developmental landmarks, if there is evidence of an endocrine mode of action. An integrated assessment with awareness of possible species-specific effects that do not predict environmental risk is expected. As examples, effects secondary to the role of inhibition or induction of drug metabolising isozymes or dopaminergic/anti-dopaminergic effects on the hypothalamo-prolactin axis would generally not be regarded as mechanisms which would warrant evaluation as an EAS.

Evidence from other sources

Evidence from scientific literature may be used. Relevant information on altered parameters includes effects on reproduction such as intersex, sex ratio and feminisation or masculinisation of fish; effects on spawning for molluscs; developmental effects on invertebrates, amphibia and/or fish. Where the evidence demonstrates that endocrine adverse effects would be expected at levels below 0.01 µg/L, the active substance should be further assessed as an EAS and the trigger value does not apply.

Tailored testing of EAS

For all EAS, the assessment depends on the mode of action (MoA) of the compound. If it can be scientifically justified, the effect assessment may be tailored to specific groups of organisms of the aquatic compartment, e.g. fish and/or amphibians. A Phase II assessment should be performed irrespective of the PEC action limit. Studies on environmental fate are required for all EAS. However, waiving of some effect tests may be applicable according to MoA, e.g. focus on specific long-term fish tests and, with justification, not include activated sludge and/or algae.

In addition to substances identified as EAS, a tailored risk assessment should also be performed for active substances where the scientific literature shows evidence of endocrine adverse effects at concentrations near or above the predicted PEC_{SW} as evidenced e.g. by intersex, sex ratio, feminisation or masculinisation, or effects at the population level in fish or amphibians. This information should be used for selecting the most appropriate chronic ecotoxicity study.

A fish early life stage test (OECD 210) may not provide the most relevant ecotoxicological information for EAS since this test is rather short and it does not cover the relevant life stages like sexual maturation and reproduction. Thus, the design of a study should include the appropriate exposure time, the sensitive life-stage(s) and the relevant endpoints necessary to detect adverse effects and underlying modes of action.

A tiered testing strategy should be followed, e.g., an in vivo screening test (OECD 229 or OECD 230) may be performed if effects on the oestrogen or androgen receptor are expected. These tests also evaluate secondary sexual characteristics in fathead minnow or medaka (OECD 229 or 230) or gonad histopathology (OECD 229). As stated in the test guidelines, both are screening tests only, and are therefore not suitable for a quantitative risk assessment. In case it is already known from e.g.

mammalian toxicity studies that estrogenic or androgenic receptors are targeted, the screening assay (OECD 229 or 230) will become redundant. If effects are observed in such a test, long-term adverse effects should then be characterised in a fish sexual development test or a fish full life cycle test. Even if the mode of action is known, it may still be necessary to perform a fish full life cycle test, for instance, when the screening or partial lifecycle tests do not cover all endpoints or life stages, which are at risk. If the mode of action or the most sensitive endpoints are not known, a fish full life cycle study should be performed.

The table below summarises tests that may be appropriate for different MoA. The applicant should develop a test proposal based on MoA considerations, possibly covering test species other than those listed below.

Table 15: Overview of recommended effect studies for active substances with an endocrine mechanism of action and thyroid hormone agonist and antagonists

Mechanism of Action	**Recommended Effect Test**
Oestrogen Receptor Agonistic	Fish full life-cycle test (DRP no. 95 /OECD 240)
Oestrogen Receptor Antagonistic	Fish sexual development test (OECD 234) or Fish full life-cycle test (DRP no. 95 / OECD 240)
Androgen Receptor Agonistic	Fish sexual development test (OECD 234) or Fish full life-cycle test (DRP no. 95 / OECD 240)
Androgen Receptor Antagonistic	Fish full life-cycle test (DRP no. 95 / OECD 240)
Aromatase Inhibition	Fish sexual development test (OECD 234) or Fish full life-cycle test (DRP no. 95 / OECD 240)
Thyroid hormone agonists and antagonists[a]	Larval amphibian growth and development assay (OECD 241)
Other mechanisms are subject to expert judgement	

[a]: Although not covered by the definition for EAS, tailored testing of thyroid hormone agonists and antagonists is recommended.

It may be appropriate to conduct a range finding study to determine the appropriate concentrations of drug substance to use in the definitive study.

If there is still uncertainty as to which test is most appropriate based on the possible mode(s) of action of compound the applicant is encouraged to seek scientific advice regarding the detailed study design, particularly before conducting fish or amphibian tests.

5. PBT assessment

PBT /vPvB substances are substances which will bioaccumulate in organisms and persist in the environment. Due to their physico-chemical characteristics, it is not possible to predict the environmental fate of these substances or the kind of adverse effects that could occur over long periods of time. Chronic exposure and long term cumulative adverse effects may lead to uncertainty when calculating the PEC via established exposure models, and/or establishing the PNEC from standard laboratory tests. Because the PBT assessment is a hazard assessment, every active substance should be assessed for its PBT properties regardless of its PEC. A tiered PBT testing strategy should be followed, beginning with a screening step in Phase I (determination of log Kow), followed by a

definitive assessment in Phase II when the trigger value of log Kow > 4.5 is met. The definitive assessment consists of sequentially testing and evaluating persistence, then bioaccumulation, then toxicity.

Annex XIII of the REACH regulation (Regulation (EC) No 1907/2006) lays down the criteria for the identification of PBT and vPvB substances (see **Table 16**). To ensure a harmonised approach, these criteria together with the methodology in the current REACH guidance on PBT-assessment (Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment and Chapters R7.a, 7.b, and R7.c on endpoints specific guidance) (ECHA 2017 a-d) should be followed. The REACH guidance documents may be obtained from the ECHA website.

For substances for which a Phase II risk assessment including assessment of the soil compartment is performed, no additional testing is required for the PBT assessment. Otherwise, a simulation degradation study in soil, water/sediment or water according to OECD guideline 307, 308, or 309 should be performed.

When log Kow for the active substance is ≥ 3, a bioconcentration factor (BCF) should be determined experimentally according to OECD 305 in order to evaluate the potential for secondary poisoning (see section 4.2.8). When this study results in a BCF-value > 2000, and the T-criterion according to **Table 16** is fulfilled, a simulation degradation study should be performed in order to check whether the substance should be classified as PBT substance. In case of a BCF-value > 5000 a simulation degradation study should be performed and evaluated against the vPvB criteria.

As for the risk assessment, the PBT assessment is performed for the environmentally relevant compound (e.g., in case of a pro-drug, the PBT assessment may be required for the active compound).

5.1. PBT Screening

A PBT screening should be performed for all active ingredients identified in the decision tree in section 4.1 (**Figure 2**), regardless of whether or not the trigger for the Phase II risk assessment is met. A PBT assessment is not required for those compounds that do not require assessment according to Q1-Q3 of the Phase I decision tree (4.1).

The PBT screening consists of the determination of an octanol/water partitioning coefficient (log Kow). In case of a dissociating compound, partitioning should be determined at three different pH values and the log D_{OW} for the neutral molecule should be determined (see section 4.2.1.1). When the trigger value of log Kow > 4.5 is met, a definitive PBT assessment should be performed.

5.2. Definitive PBT assessment

5.2.1. PBT criteria

The criteria for the assessment of P, B and T properties (**Table 16**) are specified in REACH Annex XIII.

Table 16: PBT and vPvB criteria (Annex XIII to the REACH Regulation taken from ECHA, Chapter R.11: PBT/vPvB assessment, Version 3.0 – June 2017)

Property	PBT criteria	vPvB criteria
Persistence	A substance fulfils the persistence criterion (P) in any of the following situations: (a) the degradation half-life in marine water is higher than 60 days; (b) the degradation half-life in fresh or estuarine water is higher than 40 days; (c) the degradation half-life in marine sediment is higher than 180 days; (d) the degradation half-life in fresh or estuarine water sediment is higher than 120 days; (e) the degradation half-life in soil is higher than 120 days.	A substance fulfils the "very persistent" criterion (vP) in any of the following situations: (a) the degradation half-life in marine, fresh or estuarine water is higher than 60 days; (b) the degradation half-life in marine, fresh or estuarine water sediment is higher than 180 days; (c) the degradation half in soil is higher than 180 days.
Bioaccumulation	A substance fulfils the bioaccumulation criterion (B) when the bioconcentration factor in aquatic species is higher than 2000.	A substance fulfils the "very bioaccumulative" criterion (vB) when the bioconcentration factor in aquatic species is higher than 5000.
Toxicity	A substance fulfils the toxicity criterion (T) in any of the following situations: (a) the long-term no-observed effect concentration (NOEC) or EC10 for marine or freshwater organisms is less than 0.01 mg/L; (b) substance meets the criteria for classification as carcinogenic (category 1A[2] or 1B[3]), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A[4], 1B[5] or 2[6]) according to Regulation EC No 1272/2008[7] (c) there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Regulation EC No 1272/2008.	

5.2.2. Performing the PBT assessment

The REACH guidance on PBT assessment should be followed as much as possible, and deviations should be scientifically justified. It should be noted that for the REACH PBT assessment a tiered approach is followed, since REACH chemicals do not necessarily contain all required information in the

[2] *Substances known to have carcinogenic potential for humans (epidemiological and/or animal data)*
[3] *Substances presumed to have carcinogenic potential for humans (animal studies)*
[4] *Known human reproductive toxicant (human evidence)*
[5] *Presumed human reproductive toxicant (animal studies)*
[6] *Suspected human reproductive toxicant (some evidence from humans or experimental animals, not sufficiently convincing to place the substance in category 1)*
[7] *Regulation on classification, labelling and packaging (CLP-Regulation (EC) No 1272/2008)*

dossier. Note that the screening approaches used in REACH such as ecotoxicity QSARs are not applicable to human pharmaceuticals because of the specific modes of action. In order to avoid unnecessary animal testing, testing for the P, B and T criteria is conducted sequentially. For medicinal products for which Phase II of the risk assessment is performed, most data are available (except for persistence when soil assessment is not required) and a stepwise approach is not necessary.

5.2.2.1. Persistence

If the active substance is readily biodegradable (OECD301) and is not P then no further testing is required. If this is not the case, an OECD 308 and/or OECD 307 or OECD 309 study should be performed to evaluate the P criterion. If a Phase II risk assessment is not required, a surface water simulation study (OECD 309) may be preferable. A soil simulation study (OECD 307) may be used for PBT assessment, and is required if a terrestrial risk assessment is triggered.

Persistence studies should reflect environmental temperatures in Europe and therefore preferably be conducted at 12°C. According to the REACH PBT/vPvB assessment guideline (ECHA, 2017d) if studies are conducted at different temperatures, degradation half-lives should be extrapolated to 12°C.

The Arrhenius equation is used to extrapolate degradation half-life values from the experimental temperature (e.g. 20°C) to 12°C:

$$DT50_{T1} = DT50_{T2} \times e^{\left(\frac{E_A}{R} \times \left(\frac{1}{-} - \frac{1}{T_2}\right)\right)}$$

Parameters used in the Arrhenius equation

Parameter	**Description**	**Unit**	**Default value**
$DT50_{T1}$	degradation half-life value at reference temperature	[d]	–
$DT50_{T2}$	degradation half-life value at test temperature	[d]	–
E_A	activation energy for degradation	[J mol^{-1}]	65,400
R	gas constant	[J mol^{-1} K^{-1}]	8.314
T_1	Reference temperature (12°C)	[K]	285
T_2	Test temperature (e.g. 20°C)	[K]	–

If no experimentally determined value for E_A for degradation of the active compound is available, the default value for E_A (activation energy) should be 65.4 kJ mol^{-1}[8] corresponding to a Q_{10} of 2.58, as specified in the EFSA guidance for use in FOCUS (EFSA, 2007).

For most persistent substances, removal from the aqueous phase is determined by dissipation due to partitioning to sediment rather than by true degradation. For this reason, degradation half-life values for the total system and sediment are considered most appropriate to describe the degradation half-life of a substance in the aquatic environment. Thus, half-life values for the water phase, when determined in water-sediment simulation studies, should only be used for the assessment of persistence when justified.

[8] This value is the latest revised value and should be used instead of the one recommended value in the '*CVMP/VICH revised Guideline on Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH Guidelines 6 and 38'* of 68.9 kJ mol^{-1}.

To determine degradation rates (instead of dissipation rates) the formation of non-extractable residues should not be confused with degradation. Degradation studies should be preferably performed with radio labelled compounds and using the best possible extraction methods. Only in exceptional cases may acceptable degradation data be produced using an unlabelled test substance (EMA/CVMP/ERA/349254/2014; Reflection paper on poorly extractable and/or non-radiolabelled substances), since the mass balance requirement cannot be met.

The highest sediment or total system degradation half-life value derived from the OECD 307 and/or 308 and/or 309 tests should be used for the PBT assessment.

5.2.2.2. Bioaccumulation

The results of the OECD 305 (bioaccumulation in fish) study may be used for the assessment of bioaccumulation. This study is also required for risk assessment for secondary poisoning In Phase II (section 4.2.8). Since the B criterion is based on bioconcentration in aquatic species, the test species may also be other species than fish (e.g., mussels).

It should be noted that a lack of accumulation in mammals does not automatically exclude a potential for accumulation in fish and other aquatic species. The reasons for this are decreased activity of enzymes involved in the transformation of xenobiotics in fish and/or lower trophic levels and other factors such as different exposure routes (e.g. via gills), differences in metabolism, different excretion routes, etc.

For comparison with the B and vB criteria, the measured bioconcentration value(s) (BCF) should be normalised to 5% lipid content, including a correction for growth dilution as recommended by the OECD test guideline 305 and REACH guidance (ECHA, 2017d).

Bioaccumulation studies should preferably be performed with radio labelled compounds and using the best possible extraction methods. Remaining residues in biota should be taken into account after the experimental depuration phase.

5.2.2.3. Toxicity

A substance fulfils the T criterion if it meets any of the toxicity criteria outlined in **Table 16**. Information on carcinogenicity, mutagenicity, reproductive and chronic toxicity for mammals should be available in other parts of the dossier and may also be obtained from the CLP inventory. This information should also be compared to the criteria in **Table 16**.

When toxicity data as mentioned above do not show that the compound fulfils the T criteria, for welfare reasons normally the testing order based on chronic data is algae/cyanobacteria, then Daphnia and then fish. If the T-criterion is fulfilled (**Table 16**) by the chronic algae/cyanobacteria or Daphnia data, a chronic fish test is not necessary for the PBT assessment. If further aquatic toxicity studies other than the available studies are considered necessary to conclude on the T criteria, and if there are indications that representative species from one taxonomic group are more sensitive than species from other taxonomic groups, the most sensitive group should be chosen for chronic testing.

For those substances where a Phase II assessment is triggered, sufficient toxicity studies are already available to verify whether the T criterion is met.

6. Search and evaluation of data

6.1. Data Search

If of acceptable quality, data from published literature on the active substance may be employed in the ERA as

- an alternative or supplement to the recommended standard experimental studies
- a support for a proposed tailored approach
- help with the interpretation of experimental data

To be acceptable for use in risk and/or PBT assessment, literature studies should be of sufficient reliability and include a description of all relevant aspects of the study. Besides meeting reliability criteria (see section 6.2), literature studies used as alternatives to experimental studies should be comparable in design to the recommended study designs of the studies recommended in this guideline (e.g. OECD technical guideline study designs). GLP status is not an absolute requirement for studies in the published literature.

Applicants may not refer to Public Assessment Reports (PARs or EPARs) reports or reviews or summary data from other regulatory frameworks without submitting a letter of access to the underlying studies.

6.2. Evaluation of studies

The approach used to assess the reliability and relevance of a study should be based on scientific argumentation and all studies, whatever their source, should be assessed in the same manner. A standardized assessment method designed for toxicological/ecotoxicological studies, such as the Klimisch (Klimisch et al, 1997) or CRED method (Moermond et al, 2016), is therefore recommended. All studies should be assigned a reliability category as according to the assessment method used (usually spanning 3 to 4 levels of reliability ranking), and be accompanied by a short study summary.

7. Labelling and risk mitigation

When the possibility of environmental risks cannot be excluded, specific arrangements to limit the environmental impact shall be made. The applicant should propose and to discuss a strategy for risk mitigation. Appropriate mitigation measures should generally aim at minimising the quantity discharged into the environment.

Precautionary and safety measures may consist of:

- An indication of potential risks presented by the medicinal product for the environment.
- Appropriate product storage and disposal
- Appropriate measures regarding the use of the medicinal product (e.g. to avoid the discharge of formulations such as patches and other devices into the sewage).

Precautionary and safety measures should be practical and realistic given the anticipated use of the product.

Appropriate disposal of unused pharmaceuticals, e.g. when shelf life has expired, is considered important to reduce the exposure of the environment. In order to enhance environmental protection, it is therefore recommended that – even medicinal products that do not require special disposal measures are appropriately labelled. See **Table 17**.

Additional measures:

The analytical verification of the active substance is part of the study description for the aquatic toxicity studies and some fate studies. This information is essential for water managers, who wish to monitor substances of concern. Thus, applicants are encouraged to share details on analytical verification of their active substances in the form of a report on analytical verification on their websites or in a general database, especially for those active substances with a risk to the environment. The same applies for information on fate and ecotoxicological effects as well as for any other environmental information on the active pharmaceutical substance resp. the medicinal product obtained at any time.

Table 17: Proposed labelling aimed at minimising discharge of unused medicine into the environment

ERA category	**SmPC 5.3**	**SmPC 6.6**	**Labelling (10)**	**PL (5)**
No significant risk to the environment **or** **Current ERA data do not suggest a potential risk to the environment**	No statement	Any unused medicinal product or waste material should be disposed of in accordance with local requirements.	No statement	Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.
ERA has identified a potential risk to the environment.	*Information to be driven by conclusion of the assessment e.g.:* <Environmental risk assessment studies have shown that <act.subst> has the potential to be persistent, bioaccumulative and toxic to the environment.> or <Environmental risk assessment studies have shown that <act.subst> may pose a risk for *<environmental compartment(s)>*.> (See section 6.6)	This medicinal product may pose a risk to the environment. (See section 5.3) Any unused medicinal product or waste material should be disposed of in accordance with local requirements.	No statement*	Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.*

* The actual information provided in the labelling and the PL should be considered on a case-by-case basis depending on the specific risk. In the package leaflet, this could lead to a specific advice regarding disposal. In the labelling, a relevant statement, if any, should be as short as possible, e.g. “Disposal: Read the package leaflet”.

8. Scientific advice from the EMA or national competent authorities

The applicant may request scientific 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.

9. Structure of the ERA report

The ERA report should be presented in Module 1.6 of the eCTD dossier. The full study reports and references should be provided in the annex of the ERA.

The ERA report should start with a clear identification of the active ingredient, including company name/code, IUPAC name, CAS number, empirical formula, structural formula, SMILES code, and molecular weight.

There may be cases in which the absence of environmental studies could be justified, as specified in section 4.1. In these cases, the expert should provide a rationale for the absence of studies in addition to the identification as mentioned above.

The report should contain summaries of all studies used.

A dated signature of the author, information on the author's educational, training and occupational experience, and a statement of the author's relationship with the applicant, shall be included.

10. References

EC (European Communities) (2011), Technical Guidance for Deriving Environmental Quality Standards. Common Implementation Strategy for the Water Framework Directive (2000/60/EC). Guidance Document No.27, Technical Report-2011–055.

ECETOC, 2013. Understanding the relationship between extraction technique and bioavailability. 159 Technical Report No. 117, Brussels, May 2013, ISSN-0773-8072-117.

ECHA (2016), Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.16: Environmental exposure assessment. Version 3.0, 2016

ECHA (2017a), Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.7a: Endpoint specific guidance. Version 4.0, 2017

ECHA (2017b), Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.7b: Endpoint specific guidance. Version 3.0, 2017

ECHA (2017c), Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.7c: Endpoint specific guidance. Version 3.0, 2017

ECHA (2017d), Guidance on Information Requirements and Chemical Safety Assessment: Chapter R.11: PBT/vPvB assessment. Version 3.0, 2017

Definitions

AF	Assessment factor
BCF	Bioconcentration factor
BMF	Biomagnification factor
CHMP	Committee for Medicinal Products for Human Use
CMR	Carcinogen, mutagen or reprotoxic (when chronic exposure) classification
DT50	Degradation half-life of substance (in a given compartment)
EAS	Endocrine active substance
EC10	Effective concentration representing 10% of maximum effect
EC50	Effective concentration representing 50% of maximum effect
ECHA	European Chemicals Agency
EPAR	European public assessment report
ERA	Environmental risk assessment
FELS	Fish early life stage (test)
EQS-WFD	Environmental quality standard according to the Water framework directive
FOCUS	FOrum for the Co-ordination of pesticide fate models and their USe
F_{PEN}	Market penetration factor
GLP	Good Laboratory Practice
HMP	Human medical product
Kd	Adsorption distribution coefficient
Koc	Organic carbon normalized adsorption partition coefficient
LOAEL	Lowest observed adverse effect level
Log Kow	Logarithm of octanol/water partitioning coefficient
MoA	Mode of Action ((eco)toxicological)
NOEC	No observed effect concentration
OECD	Organization for Economic Co-operation and Development
PAR	Public assessment report
PEC	Predicted environmental concentration (in a given compartment)
PNEC	Predicted no effect concentration (for a given species in a given compartment or organism)
PBT	Persistent, Bioaccumulative and Toxic (substance classification)
QSAR	Quantitative structure–activity relationship
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals

1304	RQ	Risk quotient (for a given compartment)
1305	SmPC	Summary of product characteristics
1306	STP	Sewage treatment plant
1307	vPvB	Very persistent and very bioaccumulative (substance classification)

1308