



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

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

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¹ Section 2, paragraph 5, removes the ambiguity of the word “exempt” which was meant to refer to the content of the ERA dossier and not to the legal requirement for an ERA dossier. Section 8, paragraph 2, addition of the word “studies” after ERA to clarify similarly that the guideline refers to the absence of ERA studies, not to the absence of the ERA dossier itself (expert report as a minimum).

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EXECUTIVE SUMMARY

The purpose of this guideline is to describe the assessment of potential environmental risks of human medicinal products. 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 given, and, when risks cannot be excluded, this guideline outlines precautionary and safety measures to be considered.

1 INTRODUCTION

An Environmental Risk Assessment (ERA) shall accompany an application for a marketing authorisation for a medicinal product for human use. This guideline describes how to evaluate potential risks of the medicinal product to the environment. The guideline also includes considerations for potential precautionary and safety measures to be taken, and recommendations for the 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 medicinal products should be submitted, their environmental impact should be assessed and, on a case-by-case basis, specific arrangements to limit the impact should be considered. In any event this impact should not constitute a criterion for refusal of a marketing authorisation.

An environmental risk assessment (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 evaluation of the environmental impact should be made if there is an increase in the environmental exposure, e.g. a new indication may result in a significant increase in the extent of the use. For extension applications according to Annex II of Commission Regulation (EC) No 1085/2003, an environmental risk assessment is also required if there is a potential increase in the environmental exposure, e.g. an extension application of an oral medicinal product to include a dermal patch.

An ERA is not required for renewals or Type IA/IB variations.

In the case of products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA should be provided. This ERA may consist of a justification for not submitting ERA studies, e.g. due to their nature they are unlikely to result in a significant risk to the environment. The same applies to vaccines and herbal medicinal products

In all cases, except for Type I variations and renewal applications, an environmental risk assessment or a justification for its absence should be provided in Module 1.6 of the Marketing Authorisation Application (MAA, see section 8).

Directive 2001/83/EC, as amended, relates to those risks to the environment arising from the use, storage and disposal of medicinal products and not to risks arising from the synthesis or manufacture of medicinal products. This guideline is focused on environmental risks associated with the use of medicinal products.

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/BWP/135148/04](#))”

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 96/29/Euratom and 97/43/Euratom should be taken into account.

3 GENERAL PRINCIPLES

Assessment of the potential risks to the environment is a step-wise, phased procedure, consisting of two phases. The first phase (Phase I) estimates the exposure of the environment to the drug substance. Based on an action limit the assessment may be terminated. In the second phase (Phase II), information about the fate and effects in the environment is obtained and assessed. Phase II is divided in two parts, Tier A and B (see Table I).

Certain substances, such as highly lipophilic compounds and potential endocrine disruptors, may need to be addressed irrespective of the quantity released into the environment.

Table 1: The phased approach in the environmental risk assessment

Stage in regulatory evaluation	Stage in risk assessment	Objective	Method	TEST / DATA REQUIREMENT
Phase I	Pre-screening	Estimation of exposure	Action limit	Consumption data, logKow.
Phase II Tier A	Screening	Initial prediction of risk	Risk Assessment	Base set aquatic toxicology and fate
Phase II Tier B	Extended	Substance and compartment-specific refinement and risk assessment	Risk Assessment	Extended data set on emission, fate and effects

4 PHASE I: ESTIMATION OF EXPOSURE

In phase I, the estimation should be based only on the drug substance, irrespective of its route of administration, pharmaceutical form, metabolism and excretion.

4.1 Screening for Persistence, Bioaccumulation and Toxicity

With reference to the OSPAR Convention, drug substances with a logKow >4.5 should be screened, in a step-wise procedure, for persistence, bioaccumulation and toxicity according to the EU TGD².

4.2 Calculation of the Predicted Environmental Concentration (PEC)

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

- A fraction of the overall market penetration (market penetration factor: Fpen) within the range of existing medicinal products. The Applicant may use the default value or refine the Fpen by providing reasonably justified market penetration data, e.g. based on published epidemiological data.
- The predicted amount used per year is evenly distributed over the year and throughout the geographic area.
- The sewage system is the main route of entry of the drug substance into the surface water.
- There is no biodegradation or retention of the drug substance in the sewage treatment plant (STP).
- Metabolism in the patient is not taken into account.

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

² European Chemicals Bureau (2003) Technical Guidance Document in support of Commission Directive 93/67/EEC on Risk Assessment for new notified substances, Commission Regulation (EC) No 1488/94 on Risk Assessment for existing substances and Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market.
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$$PEC_{SURFACEWATER} = \frac{DOSE_{Ei} * F_{pen}}{WASTE_{Winhab} * DILUTION}$$

Table 2: Default values for $PEC_{SURFACEWATER}$ calculation in Phase I

Parameter	Symbol	Value	Unit	Origin	Remarks
Input					
• Maximum daily dose consumed per inhabitant	DOSE _{Ei}		[mg·inh ⁻¹ ·d ⁻¹]	A	The highest recommended dose should be used
• Fraction of market penetration	F _{pen}	0.01 ^(*)	[--]	D	Default
• Amount of wastewater per inhabitant per day	WASTE _{Winhab}	200	[L·inh ⁻¹ ·d ⁻¹]	D	From TGD
• Dilution factor	DILUTION	10	[--]	D	From TGD
Output					
• Local surface water concentration	PEC _{SURFACEWATER}		[mg·L ⁻¹]	O	

A = information from Applicant, D = Default value, O = Output * see note

4.3 Action limits

If the $PEC_{SURFACEWATER}$ value is below 0.01 µg/L⁽³⁾, 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.

If the $PEC_{SURFACEWATER}$ value is equal to or above 0.01 µg/L, then a Phase II environmental fate and effect analysis should be performed as described below (section 5).

In some cases, the action limit may not be applicable. Some drug substances may affect the reproduction of vertebrate or lower animals at concentrations lower than 0.01 µg/L. These substances should enter Phase II and a tailored risk assessment strategy should be followed that addresses its specific mechanism of action. In these cases, the Applicant should justify all actions taken.

5 PHASE II: ENVIRONMENTAL FATE AND EFFECTS ANALYSIS

The recommended Phase II assessment is conducted by evaluating the PEC/PNEC ratio based on relevant environmental testing (“base set of data”) and predicted environmental concentration (Tier A). If potential environmental impact is indicated, further testing might be needed to refine PEC (predicted-environmental-concentration) and PNEC (predicted-no-effect -concentration) values in Tier B.

Experimental studies should preferably follow the test protocols issued by the European Commission, Organization for Economic Co-operation and Development (OECD) or the International Organization for Standardization (ISO). It is recognised that there are acceptable test guidelines and approaches and methods, other than those described in this section, which are capable of providing an equivalent environmental risk assessment. Their use should be justified in the Environmental Risk Assessment Report. Studies should be conducted in compliance with Good Laboratory Practices.

All relevant data should be taken into account, e.g. data on physical-chemical properties, primary and secondary pharmacodynamics, toxicology, metabolism, excretion, degradability, and persistence of the drug substance and/or relevant metabolites.

³ The present action limit is based mainly on acute toxicity data and may therefore be revised in future versions of the guideline when a sufficient amount of chronic data is available.

5.1 Tier A: Initial environmental fate and effects analysis

The assessment in Tier A should be based on the drug substance unless otherwise justified, e.g. if the drug substance is a pro-drug.

5.1.1 Physical-chemical properties and fate

The Tier A screening data set provides for information on physical-chemical properties and on the fate of a substance in the environment.

To investigate the fate of the substance in the STP a ready biodegradability test should be conducted. The fate of substances, which are not readily biodegradable, should be investigated in a water sediment study. If the K_{OW} indicates a potential for bioaccumulation, a specific risk assessment should be conducted as mentioned in Section 4.1. The sorption behaviour of substances in sewage sludge is described through the adsorption coefficient (K_{OC}), which is defined as the ratio between the concentration of the substance in the sewage sludge's organic carbon and the concentration of the substance in the aqueous phase at adsorption equilibrium. It is assumed that a substance with a high K_{OC} value is retained in the STP and may reach the terrestrial compartment with land spreading of sewage sludge.

5.1.2 Aquatic effect studies

For the Tier A assessment approach, a standard long-term toxicity test set on fish, daphnia and algae is proposed to determine the predicted no-effect concentration ($PNEC_{WATER}$). The purpose of this analysis is to predict the concentration of the substance for which adverse effects are not expected to occur. Guidance on the assessment of adverse effects is given in the TGD. The Applicant should justify the test species used.

Table 3: Physical-chemical, fate and effects studies recommended in Phase II Tier A

Study Type	Recommended Protocol
Adsorption - Desorption Using a Batch Equilibrium Method	OECD 106/ OECD 121/OPPTS 835.1110*
Ready Biodegradability Test	OECD 301
Aerobic and Anaerobic Transformation in Aquatic Sediment Systems	OECD 308
Algae, Growth Inhibition Test	OECD 201
<i>Daphnia sp.</i> Reproduction Test	OECD 211
Fish, Early Life Stage Toxicity Test	OECD 210
Activated Sludge, Respiration Inhibition Test	OECD 209

* One study is generally sufficient.

Blue-green algae (*Cyanophyta*) are recommended for effects testing of antimicrobials, as they are more sensitive indicator organisms than green algae. Short-term testing is generally not applicable for human pharmaceuticals since continuous exposure of the aquatic environment via STP effluents is assumed.

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 anti-microbial effects of anti-microbial substances, the activated sludge respiration inhibition test (OECD 209) should be used.

5.1.3 Calculation of PNEC using assessment factors

The predicted no effect concentration (PNEC) is calculated by applying an assessment factor (AF) to the no-observed-effect-concentration(s) (NOEC) from relevant effects studies. The AF is an expression of the degree of uncertainty in the extrapolation from the test data on a limited number of species to the actual environment.

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

To calculate the PNEC from the long-term toxicity tests and the anti-microbial effect study a default AF of 10 is applied. This AF accounts for:

- inter-species variations of differences in sensitivity
- intra-species variability
- laboratory data to field impact extrapolation.

5.1.4 Groundwater assessment

An exposure assessment for groundwater is required. Entry into the groundwater is considered via bank filtration, except for substances with an average $K_{\text{OC}} > 10000$ L/kg or for substances that are readily biodegradable or for substances that have a DT_{90} of < 3 days. A simple estimation is $PEC_{\text{GROUNDWATER}} = 0.25 * PEC_{\text{SURFACEWATER}}$. The $PEC_{\text{GROUNDWATER}}$ should be compared to the $PNEC_{\text{GROUNDWATER}}$.

5.2 Outcome of Tier A fate and effects analysis

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

- If the ratio $PEC_{\text{SURFACEWATER}} : PNEC_{\text{WATER}}$ for the drug substance is below 1, then further testing in the aquatic compartment will not be necessary and it can be concluded that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment.
- If the ratio $PEC_{\text{SURFACEWATER}} : PNEC_{\text{WATER}}$ is above 1, further evaluation, preferably on the fate of the drug substance and/or its metabolites in the aquatic environment are needed in Tier B.
- If the ratio $PEC_{\text{GROUNDWATER}} : PNEC_{\text{GROUNDWATER}}$ is above 1, further evaluation, preferably on the fate of the drug substance and/or its metabolites in the aquatic environment are needed in Tier B.
- If the ratio $PEC_{\text{SURFACEWATER}} : PNEC_{\text{MICROORGANISM}}$ is above 0.1, further evaluation of the fate and the effects of the drug substance and/or its metabolites on micro-organisms are needed in Tier B.
- If the n-octanol/water partition coefficient indicates the transfer of the drug substance from the aquatic environment into organisms and a potential to bioaccumulate ($K_{\text{OW}} > 1000$), then the bioconcentration factor should be considered in Tier B. Additional criteria for the need of a bioconcentration study are given in the TGD.
- If the adsorption/desorption data indicates the affinity for the drug substance to bind to sewage sludge in the STP ($K_{\text{OC}} > 10\,000$ L/kg) an environmental assessment of the drug substance in the terrestrial compartment should be conducted, unless the substance is readily biodegradable. The terrestrial risk assessment complements the aquatic risk assessment and does not replace it.
- If a substance is not readily biodegradable and if the results from the water sediment study (OECD 308) demonstrate significant shifting of the drug substance to the sediment, effects on sediment organisms should be investigated in Tier B. The criterion for sediment studies is met if more than 10% of the substance at any time point after or at 14 days is present in sediment. A detailed strategy for further testing in order to refine the PNEC for the aquatic compartment can be found in the TGD.

5.3 Tier B: Extended environmental fate and effects analysis

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

In Tier B, the refined risk assessment may be performed using the refined PEC and the PNEC for the parent compound, as well as using the dedicated PEC and PNEC for the relevant ($\geq 10\%$ of amount

excreted) metabolic fractions.

Refinement of the risk assessment using data on transformation of the substance within the environment (i.e. the water/sediment systems) is not further considered here and is subject to expert judgement.

A specific risk assessment should be conducted for a drug substance with a logKow > 4.5 (see section 4.1)

5.3.1 Environmental fate analysis and PECSURFACEWATER refinement

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

STP modelling using the SimpleTreat model described in the European Union System for the Evaluation of Substances (EUSES, <http://ecb.jrc.it/>) by incorporating:

- adsorption of substances to sewage sludge in STPs, using the data from the estimation of the adsorption coefficient (OECD 106),
- test for ready biodegradability in the STP (OECD 301).

The local surface water concentration can be refined as:

$$PEC_{SURFACEWATER} = \frac{E_{local_water} * F_{stp_water}}{WASTEWinhab * CAPACITY_{stp} * FACTOR * DILUTION}$$

Where

$$E_{local_water} = DOSE_{ai} * F_{excreta} * F_{pen} * CAPACITY_{stp}$$

Table 4 summarises the parameters and default values recommended for the calculation of $PEC_{SURFACEWATER}$ in Phase II. Worst-case estimates should be used.

Table 4: Parameters and defaults for $PEC_{SURFACEWATER}$ calculation in Phase II

Parameter	Symbol	Value	Unit	Origin	Remarks
Input					
• Amount of wastewater per inhabitant per day	<i>WASTEWinhab</i>	200	[L·inh ⁻¹ ·d ⁻¹]	D	From TGD
• Capacity of local sewage treatment plant (STP)	<i>CAPACITY_{stp}</i>	10000	[inh]	D	From TGD
• Fraction of emission directed to surface water	<i>F_{stp_{water}}</i>		[--]	C	Calculated by SimpleTreat
• Dilution factor	<i>DILUTION</i>	10	[--]	D	From TGD
• Factor taking the adsorption to suspended matter into account	<i>FACTOR</i>		[--]	C	From TGD §2.3.8.3
• Local emission to wastewater of the relevant residue	<i>E_{local_{water}}</i>		[mg d ⁻¹]	A	
Output					
• Local surface water concentration	<i>PEC_{local_{water}}</i>		[mg·L ⁻¹]	O	

A = information from Applicant; D = Default, C = Calculated, O = Output

5.3.2 Extended effects analysis

5.3.2.1 Water sediment effects

Effects on a sediment dwelling organism (*Hyalella* sp; *Lumbriculus* sp. or *Chironomus* sp.) should be investigated and compared to the PEC_{SEDIMENT} if the results from the water sediment study (OECD 308) demonstrate significant shifting of the drug substance to the sediment.

5.3.2.2 Specific effects on micro-organisms

If in Tier A, a risk for micro-organisms is identified, further evaluation of the fate and effects of the drug substance and/or its metabolites on micro-organisms are needed in Tier B.

The exposure concentration in the aeration tank of the SimpleTreat model ($PEC_{\text{AERATION TANK}}$) should be used to refine the risk quotient for micro-organisms. To determine the $PNEC_{\text{MICROORGANISMS}}$ a number of standardized tests on single microbial species are given in the TGD (e.g. *Pseudomonas putida*). If the ratio $PEC_{\text{AERATION TANK}} : PNEC_{\text{MICROORGANISMS}}$ is >1 , further analyses of anti-microbial effects should be conducted in Tier B.

5.3.3 Terrestrial environmental fate and effects analysis

When indicated ($K_{\text{OC}} > 10000$ L/kg), unless readily biodegradable, the concentration of the medicinal product in the terrestrial compartment should be calculated. STP modelling to obtain a PEC_{SLUDGE} is performed using the SimpleTreat model in EUSES (<http://ecb.jrc.it/>). Methodologies, such as described in the TGD, should preferably be used for risk assessment including PEC_{SOIL} calculation.

In general, a base set of tests investigating biodegradation in soil, toxicity to soil invertebrates and acute effects on terrestrial plants and micro organisms should be conducted (Table 5).

Table 5: Terrestrial fate and effects studies recommended in Phase II Tier B:

Study Type	Recommended Protocol
Aerobic and anaerobic transformation in soil	OECD 307
Soil Micro organisms: Nitrogen Transformation Test	OECD 216
Terrestrial Plants, Growth Test	OECD 208
Earthworm, Acute Toxicity Tests	OECD 207
<i>Collembola</i> , Reproduction Test	ISO 11267

5.4 Outcome of Tier B fate and effects analysis

At the end of Tier B, information from the refined data set is available comprising information on route(s) of excretion and qualitative and quantitative information on excreted compounds, and possibly additional long-term toxicity data, additional data on microbial inhibition, and additional information on the biodegradability of the substance.

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

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

- An indication of potential risks presented by the medicinal product for the environment.
- Product labelling, Summary Product Characteristics (SPC), Package Leaflet (PL) for patient use, product storage and disposal.

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

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

measures - package leaflets (patient information leaflets) should include the following general statement:

“Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.”

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

7 SCIENTIFIC ADVICE FROM THE CHMP

The applicant may request scientific advice on issues related to environmental risk assessment and on possible precautionary and safety measures to be taken with respect to the use and disposal of a medicinal product.

8 THE ENVIRONMENTAL RISK ASSESSMENT REPORT

The Expert Report should be presented in Module 1.6 of the dossier. The report should be based on the characteristics of the product, its potential environmental exposure, fate and effects, and risk mitigation strategies as appropriate. The conclusion of the report should be based on sound scientific reasoning supported by adequate studies. If other relevant data are available they should also be submitted, e.g. tests focussing on relevant substance specific biological effects.

There may be cases in which the absence of ERA studies could be justified (e.g. marketing authorisation applications for generic medicinal products or type II variations). In these cases, the expert should provide a rationale for the absence of ERA studies, taking into consideration a possible significant increase of environmental exposure to the drug substance.

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

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

The expert should sign the Expert Report and a curriculum vitae should be provided.

9 Note

Fpen

A 95 percentile of 0.954 % was calculated as the default penetration factor (Fpen). It is proposed to use an Fpen of 0.01 (1%) in the risk assessment.

The penetration factor (Fpen) represents the proportion of the population being treated daily with a specific drug substance. The default penetration factor was derived from a wide range of individual market penetration factors, which were calculated as follows:

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

The following data were used:

- Institut für Medizinische Statistik, Frankfurt/M., (IMS Health): IMS Health maintains a data bank “Chemical Country Profil” containing statistics for annual German consumption of about 2700 drug substances. This database was considered representative for the drug consumption in the European Union.
- Defined daily dose values (DDD) values of the World Health Organization (WHO). In total DDD-values for about 1450 drug substances were available.
- German population: 82 012 000 inhabitants in 2001

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

10 LIST OF ABBREVIATIONS

AF	Assessment Factor
CHMP	Committee for Medicinal Products for Human Use
DDD	Defined daily dose value(s)
DT90	Degradation Time for 90% of a substance to be degraded under laboratory conditions
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EUSES	European Union System for the Evaluation of Substances
Fpen	(Market) Penetration Factor (see note 1)
GMOs	Genetically Modified Organisms
ISO	International Organization for Standardization
Koc	Adsorption Coefficient
MAA	Marketing Authorisation Application
NOEC	No Observed Effect Concentration
OECD	Organization for Economic Co-operation and Development
OPPTS	US EPA Office of Prevention, Pesticides and Toxic Substances
OSPAR	1992 Convention for the Protection of the Marine Environment of the North-East Atlantic (The “OSPAR Convention”)
PEC	Predicted Environmental Concentration

PNEC	Predicted No Effect Concentration
PL	Package Leaflet
SPC	Summary of Product Characteristics
STP	Sewage Treatment Plant
TGD	EU Technical Guidance Document
WHO	World Health Organization

11 ANNEX

