Environmental classification of pharmaceuticals at www.fass.se

Guidance for pharmaceutical companies

2025 v 1.0

The research-based pharmaceutical industry

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Introduction

The Swedish environmental classification of pharmaceuticals has been presented at www.fass.se since October 2005. At present time, most of the pharmaceuticals have environmental information published at the website.

Lif, the trade association for the research-based pharmaceutical industry in Sweden, took the initiative to develop a voluntary environmental classification scheme, in partnership with other interested parties in the healthcare sector. The purpose is a transparent model available to the public, the healthcare sector, and researchers.

The environmental information, focusing on the aquatic environment, is based on data from the pharmaceutical companies but is reviewed by an independent party, IVL Swedish Environmental Research Institute.

Since the start in 2005, the guidance has been updated in 2007, 2012 and a minor update in 2021. It is intended that the classification scheme will be reviewed on an on-going basis and may be subject to future refinement, based on developing scientific principles, new data, and regulatory guidance. This current update is brought on by the update of the EMA Guideline (Ref 1), which came into effect in September 2024. The changes to this guidance have been reviewed by both Lif and IVL.

Definitions and abbreviations

AF	assessment factor
API	active pharmaceutical ingredient
BCF	bioconcentration factor
DO	dissolved oxygen
DOW	octanol/water distribution coefficient
ECHA	European Chemicals Agency
EMA	European Medicines Agency
ERA	environmental risk assessment
EAS	endocrine active substance
FDA	US Food and Drug Administration
KOW	octanol/water partition coefficient
MEC	measured environmental concentration
NER	non-extractable residues
NOEC	no observed effect concentration
OECD	The Organization for Economic Cooperation and Development
PEC	predicted environmental concentration
PBT	persistent, bioaccumulative and toxic
PNEC	predicted no effect concentration
STP	sewage treatment plant
vPvB	very persistent and very bioaccumulative
QSAR	quantitative structure–activity relationship models

1. Presentation of Environmental Information at www.fass.se

www.fass.se is the Swedish medicines information portal. The portal is open to the public. In the environmental tab called “Miljöinfo” the environmental information is presented for the active pharmaceutical ingredients (APIs) for each product, (Fig. 1).

The first level of environmental information contains summary phrases about the environmental risk, degradation, and bioaccumulation. The next level, when “läs mer” is chosen, contains detailed background information directed to people specifically interested in the environmental data and the underlying basis of the risk assessment.

Please note that the summary phrases are given in Swedish at www.fass.se, although English translations are available in this document for comparison. However, the detailed background information can be given in English.

Figure 1. The environmental tab “Miljöinfo” at www.fass.se.

1.1. Summary phrases: Environmental risk, degradation and bioaccumulation

The first level of information provides summary phrases based on aquatic environmental risk, degradation and bioaccumulation. The environmental risk phrase (Table 1) is based on the PEC/PNEC ratio (Predicted Environmental Concentration / Predicted No Effect Concentration) of the API. The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase (to be given in Swedish at www.fass.se).

1.1.1. Environmental risk

The summary phrases for environmental risk are given in Table 1. For information on how to calculate the environmental risk, see further chapter 2.2.

Table 1. Summary phrases for the environmental risk.

Environmental risk		
PEC/PNEC ratio	**Summary phrase, English**	***Summary phrase, Swedish***
PEC/PNEC ≤ 0.1	Use of [name of the substance] has been considered to result in insignificant environmental risk.	*Användning av [substansnamnet] har bedömts medföra försumbar risk för miljöpåverkan.*
0.1 < PEC/PNEC ≤ 1	Use of [name of the substance] has been considered to result in low environmental risk.	*Användning av [substansnamnet] har bedömts medföra låg risk för miljöpåverkan.*
1 < PEC/PNEC ≤ 10	Use of [name of the substance] has been considered to result in moderate environmental risk.	*Användning av [substansnamnet] har bedömts medföra medelhög risk för miljöpåverkan.*
PEC/PNEC > 10	Use of [name of the substance] has been considered to result in high environmental risk.	*Användning av [substansnamnet] har bedömts medföra hög risk för miljöpåverkan.*
If there is no data to calculate the PEC/PNEC.	Risk of environmental impact of [name of the substance] cannot be excluded, since no ecotoxicity data are available.	*Risk för miljöpåverkan av [substansnamnet] kan inte uteslutas då ekotoxikologiska data saknas.*
If there is some, but not sufficient data to calculate the PEC/PNEC.	Risk of environmental impact of [name of the substance] cannot be excluded, since there is not sufficient ecotoxicity data available.	*Risk för miljöpåverkan av [substansnamnet] kan inte uteslutas då det inte finns tillräckliga ekotoxikologiska data.*
If PEC/PNEC <1 but the substance is flagged as a potential PBT or vPvB substance[1]	Hazardous environmental properties.	*Särskilt miljöfarliga egenskaper.*

[1] See Section 2.5 and Table 13.

For some APIs, data may be lacking due to limited use or low dose which, in turn, means the action limit in the EMA guideline (Ref. 1) of PEC < 0.01 µg/L is not triggered and, consequently, an environmental risk assessment may not have been undertaken. In these cases, the following phrase should be included in the detailed background information (to be given in English or Swedish):

In English:

According to the European Medicines Agency Guideline on environmental risk assessment of medicinal products (EMA/CHMP/SWP/4447/00 Rev. 1), use of [name of the substance] is unlikely to represent a risk for the environment, because the predicted environmental concentration (PEC) at the time of registration was below the action limit 0.01 µg/L.

In Swedish:

Enligt den europeiska läkemedelsmyndigheten EMA:s riktlinjer för miljöriskbedömning av läkemedelssubstanser (EMA/CHMP/SWP/4447/00 Rev. 1), bedömdes det vid registreringstillfället vara osannolikt att användningen av [substansnamnet] kommer att medföra en miljörisk, då det förväntas att användningen ger en koncentration i miljön (PEC) som bli lägre än tröskelvärdet 0,01 µg/L.

1.1.2. Degradation

The summary phrases for degradation are given in Table 2. For information on how to calculate the degradation potential, see further chapter 2.3.

Table 2. Summary phrases for degradation.

Degradation	
Summary phrase, English	***Summary phrase, Swedish***
[Name of the substance] is degraded in the environment	*[Substansnamnet] bryts ned i miljön.*
[Name of the substance] is slowly degraded in the environment	*[Substansnamnet] bryts ned långsamt i miljön.*
[Name of the substance] is potentially persistent	*[Substansnamnet] är potentiellt persistent.*
The potential for persistence of [name of the substance] cannot be excluded, due to lack of data.	*Det kan inte uteslutas att [substansnamnet] är persistent, då data saknas.*

For substances classified as PBT/vPvB, no summary phrase for degradation is given. Instead, the phrase *"According to the established EU criteria, [name of the substance] should be regarded as a PBT/vPvB substance." is given under the headline "PBT/vPvB-klass"* (see chapter 2.5).

1.1.3. Bioaccumulation

The summary phrases for bioaccumulation are given in Table 3. For information on how to calculate the bioaccumulation potential, see further chapter 2.4.

Table 3. Summary phrases for bioaccumulation.

Bioaccumulation	
Summary phrase, English	***Summary phrase, Swedish***
[Name of the substance] has low potential for bioaccumulation.	*[Substansnamnet] har låg potential att bioackumuleras.*
[Name of the substance] has high potential for bioaccumulation.	*[Substansnamnet] har hög potential att bioackumuleras.*
The potential for bioaccumulation of [name of the substance] cannot be excluded, due to lack of data.	*Det kan inte uteslutas att [substansnamnet] kan bioackumuleras, då data saknas.*

For substances classified as PBT/vPvB no summary phrase for bioaccumulation is given. Instead, the phrase “According to the established EU criteria, [name of the substance] should be regarded as a PBT/vPvB substance.” is given under the headline “PBT/vPvB-klass” (see chapter 2.5).

1.2. Exempted substances

According to the EMA Guideline on the environmental risk assessment of medicinal products (Ref. 1), vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents.

However, peptides and proteins that have been structurally modified using non-natural amino acids to increase biostability are considered non-natural. For non-natural peptides/proteins, an additional screening step should be performed to demonstrate that they will be quickly degraded in the sewage treatment plant (STP) and will not enter the environment. Non-natural peptide/protein demonstrated to be excreted in amounts < 10% of the dose or shown to be readily biodegradable in an OECD 301 test, can be regarded as exempted.

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

Pharmaceuticals which have an antibacterial mode of action or that are endocrine active substances, are not considered exempted (see sections 1.3.1 and 1.3.2 below).There might be other pharmaceuticals on the Swedish market that could be exempted due to the nature of their constituents e.g. activated carbon. In these cases, the companies should supply the reviewer with enough information to justify the exemption. Substances that, due to their volatility or other physical parameters, cannot be assessed for aquatic environmental fate and effects are also exempted. The justification of the exemption should be included in the detailed background information.

For substances in the category “Others” (see Table 4) a brief justification as to why it belongs to that category must be presented.

No environmental information will normally be provided for the exempted pharmaceuticals, and the following summary phrases (Table 4) will be used in the first level of information.

Table 4. Summary phrases for exempted substances

Exempted substances		
Substance	**Summary phrase, English**	***Summary phrase, Swedish***
Vitamins	Use of vitamins has been considered to result in insignificant environmental impact.	*Användning av vitaminer bedöms inte medföra någon miljöpåverkan.*
Electrolytes	Use of electrolytes has been considered to result in insignificant environmental impact.	*Användning av elektrolyter bedöms inte medföra någon miljöpåverkan.*
Amino acids, proteins and peptides	Use of amino acids/peptides/proteins has been considered to result in insignificant environmental impact.	*Användning av aminosyror/peptider/proteiner bedöms inte medföra någon miljöpåverkan.*
Carbohydrates	Use of carbohydrates has been considered to result in insignificant environmental impact.	*Användning av kolhydrater bedöms inte medföra någon miljöpåverkan.*
Lipids	Use of lipids has been considered to result in insignificant environmental impact.	*Användning av lipider bedöms inte medföra någon miljöpåverkan.*
Vaccines	Use of vaccines has been considered to result in insignificant environmental impact.	*Användning av vacciner bedöms inte medföra någon miljöpåverkan.*
Herbal Medicinal Products	Use of herbal medicinal products has been considered to result in insignificant environmental impact.	*Användning av växtbaserade läkemedel bedöms inte medföra någon miljöpåverkan.*
Others, including nucleotides	Use of [name of the substance] has been considered to result in insignificant environmental impact.	*Användning av [substansnamnet] bedöms inte medföra någon miljöpåverkan.*

The reviewer may request additional information from companies to justify the exemption and ensure consistency in the approaches used. The justification for an exempted substance should also be given in the detailed background information. If the exemption refers to the EMA guideline (Ref. 1) the detailed background information should also include the following reference phrase (to be given in English or Swedish):

In English:
According to the European Medicines Agency guideline on environmental risk assessments of medicinal products (EMA/CHMP/SWP/4447/00 Rev. 1), vitamins, electrolytes, amino acids, peptides, proteins, nucleotides, carbohydrates, lipids, vaccines and herbal medicinal products are exempted because they are unlikely to result in significant risk to the environment.

In Swedish:
Enligt den europeiska läkemedelsmyndigheten EMA:s riktlinjer för miljöriskbedömning av läkemedelssubstanser (EMA/CHMP/SWP/4447/00 Rev. 1), är vitaminer, elektrolyter, aminosyror, peptider, proteiner, nukleotider, kolhydrater, lipider, vacciner och växtbaserade läkemedel undantagna då de inte bedöms medföra någon betydande risk för miljön.

Depending on the characteristics of the exempted substance, the reviewer may request full environmental information from companies even though the substance is exempted according to the EMA guideline (Ref. 1).

1.2.1. Biologically active substances

Biologically active substances are likely to express similar pharmacological response in biota as their mode of action in humans. Considering that, the justification of the exemption assessed as being biologically active should be supplemented with the following phrase (to be given in English or in Swedish):

In English:
Even though biomolecules are exempted from environmental risk classification it should be remembered that these molecules may be biologically active.

In Swedish:

Även om biomolekyler är undantagna från miljöriskklassificering bör det beaktas att dessa molekyler kan vara biologiskt aktiva.

1.3. Antibacterials and endocrine active substances

1.3.1. Antibacterials

If the active substances have an antibacterial mode of action, and the PEC exceeds the action limit (> 0,01 µg/L), a tailored assessment should be performed. Scientific knowledge and empirical data justify a testing strategy focused on the effects on lower trophic levels including bacteria, algae and aquatic invertebrates. Cyanobacteria are more appropriate than green alga, and fish tests are not required (see EMA Guideline sections 4.2.1.3 and 4.3.1, Ref. 1).

1.3.2. Endocrine active substances

Endocrine active substances (EAS) are substances that can interact or interfere with normal hormonal action. EAS can have effect on reproduction or development at concentrations below the action limit (0,01 µg/L) and can exert effect by directly interacting or interfering with receptors,

hormone levels or activities of oestrogens, androgens, thyroid hormones or other steroid hormones. An active substance whose intended pharmacological action targets the endocrine system is considered to be an EAS. An assessment to determine the risk ratio (PEC/PNEC) should be performed for all EAS regardless of the PEC. The mode of action of the substance determines the choice of study to perform and the assessment can be tailored to specific groups of organisms, e.g. fish or amphibians. For further information see EMA Guideline section 4.3.2 (Ref. 1).

1.3.3. Antiparasitics

Substances with an antiparasitic mode of action should, like antibiotics, be assessed for ecotoxicity regardless of whether the PEC exceeds the action limit or not. But no tailored testing is necessary.

1.4. Detailed background information

Detailed environmental information and the underlying basis of the risk assessment can be found under the link “Läs mer” (“Read more”) at fass.se. Please see section 2.1 Data Collection for guidance on which information to include, and Appendix 1 for an example on how to present data.

Please note that in some cases the detailed background information should include a justification of an exempted substance (see 1.2) or a clarification of why environmental data is lacking (see 1.1.1).

1.5. Data sharing

Companies are encouraged to share their data, to minimise the number of tests performed and in accordance with the 3R principles (replace, reduce, refine). For APIs that are already on the market, a new manufacturer should use all relevant data that is available on public domains and from other companies.

A mechanism for data sharing, review and publication within the Fass database is available e.g. for generic compounds.

Companies lacking their own environmental data for the APIs can link to the environmental information produced by another company. In that case the text in Table 5 will automatically appear below the headline ”Environmental impact/Miljöpåverkan”.

Table 5. Information presented in case of data sharing.

English phrase for data sharing	*Swedish phrase for data sharing*
Environmental information for [name of the substance] originates from [name of the company] for [product name].	*Miljöinformation för [substansnamnet] är framtagen av [företagsnamnet] för [produktnamnet].*

If the original manufacturer no longer markets the compound, and the information for that product no longer is available on fass.se, the generic manufacturer can ask for permission to use environmental data from the original manufacturer.

1.6. Referencing

References, internal (e.g. company technical reports) or external (publicly available reports and publications), should be given in association with all the submitted data and in a reference list in the end of the detailed background information. Preferably references to original data should be presented and references to safety data sheets should be avoided. The reference should include year of publication and if adequate a version number. On request by the reviewer, additional information should be provided to clarify the data. Confidentiality will be maintained where appropriate.

2. How to assess environmental risk, degradation and bioaccumulation

The following sections describes how to collect data. See Appendix 1 for an example of how to present data.

2.1. Data Collection

It is advisable that the main excreted active form is assessed. If these data are not available, data for the parent compound should be used. For combination products, each active ingredient should be assessed.

It is preferred to use experimental data rather than estimated data (e.g. measured ecotoxicity/D_{ow} vs QSAR). If estimated data are used, the company should justify the scientific rationale.

Environmental information on pharmaceutical compounds published in scientific peer reviewed journals has become more available during the last few years. To make sure all relevant data are considered, companies should take into account relevant published data when evaluating the environmental risk and hazard of the API. The environmental test results, together with the test guidelines followed (OECD, FDA etc.), should be presented. If the test is not standardized, see 2.2.4, 2.3.4, 2.4.1 and Appendix 2 for further guidance.

In some cases, the reviewer may request additional information from companies to ensure consistency in the approaches used.

2.1.1. The following information, where available, should be used when classifying the APIs

- **Sales data** in kilograms of API in Sweden should be taken into account, including all products and enantiomers containing the same API and all salts of the API (e.g. metoprolol succinate and metoprolol tartrate). If the salt-part (the counter-ion) is subtracted from the total amount this should be explained in the document.
  - For marketed products, data from the most recent year will be provided by Lif in Sweden through cooperation with IQVIA.
  - For newly introduced products (on patent), it is recommended to use the forecasted sales five years after launch when calculating the environmental risk. If forecasted sales data are confidential, it is allowed to calculate a theoretical interval of quantity substance, based on the environmental risk class to be used, and thereafter state that the forecasted sales in kg are between the limits of this interval.
- **Excretion of parent compound** after use, as % of given dose.

- **Excretion of metabolites** after use, as % of given dose, including:
  - Identification of the metabolites, including specification of conjugates, which may deconjugate to the parent compound in an STP.
  - Pharmacological activity (or ecotoxicity, if known) of the metabolites compared with the parent compound.
- **Short-term and long-term effects data** for algae, crustaceans (usually *Daphnia magna* or *Ceriodaphnia dubia*) and fish. Please provide detailed information about tests e.g.
  - Test guideline,
  - type of test (e.g. acute toxicity or chronic toxicity),
  - test duration,
  - endpoint and species names both in Swedish (or English) and in Latin. Note that growth rate (not yield/biomass) should be used as endpoint in the Algae growth inhibition test OECD 201 according to ECHA Guideline R7b, page 31 (Ref. 3).
- **Risk assessment**, i.e. PEC/PNEC, calculations as well as the specific PEC and PNEC calculation, given in µg/L, where applicable
- **Biodegradation**: Ready biodegradability and/or other relevant biodegradation studies where the biomass has not been deliberately pre-exposed to the parent compound (see EMA Q&A, Q 8, p. 5 (Ref. 7)).
- **Abiotic degradation**: photolysis, hydrolysis, volatilization
- Identification of **primary transformation products** >10%, where applicable
- **Adsorption** to **sewage sludge** (K_{oc}, Kd_{sludge})
- **Monitoring data** showing STP removal and/or concentrations in the environment. If any of these data are used, the company should justify the scientific rationale. In some cases, the reviewer may request additional information from companies to ensure consistency in the approaches used.
- **The bioconcentration factor** (BCF), and/or **partition coefficient** log K_{ow} (often referred to as log P_{ow} or log P). Log D_{ow} or log D_{lipw} can also be used if appropriate.

All data should, where possible, follow the appropriate OECD, FDA or similar guidelines. Table 6 shows some comparable test guidelines.

Table 6. Some comparable OECD and FDA test guidelines.

Test	OECD guideline	FDA guideline
Algal growth inhibition	201	4.01
D. magna, acute toxicity	202	4.08
D. magna, chronic toxicity	211	4.09
Fish, acute toxicity	203	4.11
Hydrolysis	111	3.09
Soil sorption/desorption	106	3.08
Ready biodegradability	301	3.11
Inherent biodegradability	302	3.12

2.2. Environmental Risk Assessment (ERA)

To assess the environmental risk of an API, the PEC and the PNEC values need to be calculated. The environmental risk is estimated by calculating the PEC/PNEC ratio. This defines the appropriate risk phrase to be used in the classification scheme, see section 1.1.

2.2.1. Predicted Environmental Concentration (PEC)

The PEC (expressed in µg/l) is obtained by using the following formula, and is based on the total sales of the API in kg/year in Sweden:

Equation

$$PEC = \frac{A * 10^9 * (100 - R)}{365 * P * V * D * 100} = 1{,}37 * 10^{-6} * A * (100 - R)$$

The parameters used in the equation are described in table 7.

The factor 10^9 in the equation converts the quantity used from kg to µg. The factor 365 in the denominator in the equation converts from annual to daily quantity used. Simplifying all the default values into a single factor gives the second part of the equation.

Table 7. Parameters used in the equation for calculating PEC. Default value for V and D are taken from Guidance on information requirements, chapter R. 16 (Ref. 5).

Parameters used in the equation			
Parameter	**Unit**	**Description**	**Default value**
A	kg/year	total actual API sales (active moiety) in Sweden for the most recent year. Will be obtained from Lif.	-
R	%	removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation)	0 if no data is available
P		number of inhabitants in Sweden	10×10^6
V	L/day	volume of wastewater per capita and day	200
D		factor for dilution of wastewater by surface water flow	10

2.2.1.1. Metabolism

The PEC calculation can consider the extent of metabolism of the active moiety to less pharmacologically active or inactive compounds, e.g. kg x 10% x 0.5 for a metabolite found at a level of 10% and that has half the pharmacological activity of the main active ingredient. This is effectively the same as the FDA approach (Ref. 6). Note, if human metabolism and pharmacological activity of the metabolites are used to refine the PEC calculation, then sufficient data should be provided to support the assumptions made. Specifically, both the amount of metabolite present (as a fraction of excreted material) and the relative pharmacological activity compared to the main active moiety should be provided. It should not be assumed that human metabolites are inactive without supporting information.

If there is uncertainty about the relative potency of metabolites, or the amounts excreted, it is recommended to assume that 100% is excreted as the active parent molecule. This is considered to represent a reasonable worst case.

2.2.1.2. Sewage Treatment Plant removal

STP simulation studies (e.g. OECD 303) can be used directly for predicting removal during sewage treatment. If Ready or Inherent biodegradability test results are available (OECD 301 and 302 series), the SimpleTreat model may be used to calculate removal during sewage treatment (see Ref. 5, Appendix R.16-3). It is recommended to use SimpleTreat, but alternative models may be used if reasonably justified.

If an OECD 308 study is available and demonstrates >60% mineralization (or 90% primary degradation) by the end of the 100 days test period, it is considered reasonable to assume that the substance would be readily removed in an STP. When using SimpleTreat to calculate the removal rate and these criteria are met, the substance may be regarded as “readily biodegradable but failing the 10d window”.

2.2.1.3. Measured Environmental Concentration (MEC)

In principle it should be possible to use measured concentrations (MEC) instead of predicted environmental concentrations if such data are sufficient to ensure a representative exposure assessment. Adequate supporting information should be provided to justify the interpretation of the results. In some cases, the reviewer may request additional information from companies to ensure consistency in the approaches used. In the detailed background information, it is recommended to present both the MEC and PEC figures to enable comparison.

2.2.2. Predicted No Effect Concentration (PNEC)

Ideally, chronic ecotoxicological data should be provided for three trophic levels (usually algae, crustaceans (*D. magna* or *C. dubia*) and fish. The EC10 is preferred over the NOEC for PNEC derivation. If chronic data is lacking, acute ecotoxicity data may be used. If relevant data are available for the species believed to be most sensitive, based on an understanding of receptor-mediated effects for example, then it may still be possible to derive a PNEC with data from only one or two species. For antibacterials, e.g., ecotoxicological data from lower trophic levels are more relevant (usually bacteria, algae and aquatic invertebrates). See also section 1.3.1 on antibacterials.

If a valid PNEC cannot be calculated, the phrases; “Risk of environmental impact of [name of the substance] cannot be excluded, since no ecotoxicity data are available” or “Risk of environmental impact of [name of the substance] cannot be excluded, since there is not sufficient ecotoxicity data available” should be used (see Table 1).

2.2.2.1. Assessment Factors

The PNEC should be obtained by applying assessment factors (AF) to chronic ecotoxicity data in accordance with the ECHA guidance (Ref. 2, Table R.10-4). An AF of 1000 is normally applied to the most sensitive of three acute toxicity tests (LC/EC_{50}) if results from three trophic levels are available. However, the AF may be reduced to 100, 50 or 10, depending on the number of chronic EC_{10} or NOEC endpoints available, providing chronic data are available for the species with the lowest acute LC/EC_{50}.

The AF recommended in the ECHA guidance may not always be applicable, e.g. if particularly sensitive species are identified, based on evaluation of the mode of action of the API, or if mammalian toxicology or data from similar compounds indicate that a higher or a lower AF would be more appropriate. This needs to be considered on a case-by-case basis, with justification provided for the AF used. For instance, cyanobacteria (*Cyanophyceae*) are recommended for effects testing of antimicrobials (see EMA guideline, Ref. 1). If a full data set of a cyanobacteria study, a green alga study and the chronic *Daphnia* study are conducted an AF of 10 can be applied.

2.2.3. Use of non-standard data in the ERA

If the test is not standardized, this should be noted, and the company should provide enough information to facilitate interpretation of the results by an independent reviewer and other interested parties. This includes type of endpoint and its ecological relevance, but also other relevant information such as test medium, temperature, exposure regime, number of replicates and test geometry (see Appendix 2 for further information).

2.3. Assessment of degradation

This section describes how to assess the degradation potential of the APIs. The phrase for degradation presented at fass.se is not necessarily related to the “P” criterion in a PBT/vPvB assessment according to REACH (Refs. 10 and 4). For more information on PBT/vPvB assessment, see section 2.5.

Persistence is characterized by the potential for a substance to remain undegraded or unchanged in the environment. Degradation mechanisms can be biotic (biodegradation) and/or abiotic.

Tests on ready and inherent biodegradability contribute information at a screening level whereas simulation tests are adequate to assess degradation kinetics, degradation half-lives, information about mineralisation, non-extractable residues (NERs) and transformation/degradation products (extracted residues). In practice, biodegradation in the environment is normally extrapolated from laboratory experiments such as Ready tests (e.g. OECD 301 series), Inherent tests (OECD 302 series) or simulation studies (OECD 303/307/308/309). Mineralisation reduces a pharmaceutical to its basic constituents, which are considered to present no significant environmental risk.

Primary degradation of a molecule might also significantly reduce or eliminate its pharmacological activity. In such cases, information should be provided to demonstrate the expected reduction in ecotoxicity. This might be based on direct measurement or, if the identity of the transformation product is known and a suitable analytical standard exists, on a comparison with human metabolites and their relative pharmacological activity, for example.

2.3.1. Interpretation of biodegradation studies (ready and inherent)

If a substance passes the criteria for ready biodegradability, as defined in the OECD 301 test guideline series (or equivalent), the substance is considered not persistent, and no further testing is required.

The pass levels for ready biodegradability are 70% removal of DOC and 60% of ThOD or ThCO2 production for respirometric methods. These pass values must be reached in a 10-day window within the 28-day period.

The pass criteria and summary phrases for degradation, based on OECD 301, are presented in Table 8.

Table 8. Summary of pass criteria for degradation phrases based on OECD 301.

Pass criteria	Summary phrase
The substance passes the criteria for “ready” biodegradability.	[Name of the substance] is degraded in the environment.
The substance does not pass the criteria for ready biodegradability but the test shows significant mineralisation.	[Name of the substance] is slowly degraded in the environment.
If a substance fails to meet the above criteria, and there are no other simulation studies or analytical monitoring data to support elimination/degradation	[Name of the substance] is potentially persistent.

If the substance is confirmed to degrade in other biodegradation tests than the tests for ready biodegradability, the results may be used to indicate that the substance will not persist in the environment. If a substance passes the criteria below for inherent biodegradability, as defined in the ECHA Guidance Table R. 11-4 (Ref 4), see table 9 for degradation phrases.

- Zahn-Wellens test (OECD 302B): pass level - 70% mineralisation in 7 days, log-phase no longer than 3 days, percent removal in the test before degradation occurs < 15%, not tested with pre-adapted inoculum
- MITI II test (OECD 302C): pass level - 70% mineralisation should be reached within 14 days, log-phase no longer than 3 days, not tested with pre-adapted inoculum

Table 9. Summary of pass criteria for degradation phrases based on OECD 302.

Pass criteria	Summary phrase
The substance passes the criteria for "inherent" biodegradability, as defined in the ECHA Guidance Table R. 11-4 (Ref 4)	[Name of the substance] is slowly degraded in the environment.
If a substance fails to meet the above criteria, and there are no other simulation studies or analytical monitoring data to support elimination/degradation	[Name of the substance] is potentially persistent.

2.3.2. Interpretation of simulation studies

Tests on simulation degradation and transformation (OECD TG 309 surface water, OECD TG 308 sediment or OECD TG 307 soil) are adequate to assess degradation kinetics, degradation half-lives, information about mineralisation, non-extractable residues (NERs) and transformation/degradation products (extracted residues).

Fundamentally, data generated from an OECD 308 study are not suitable for generating independent water and sediment half-lives because the test system represents a dynamic interaction between the two compartments. Furthermore, the presence of bound (unextractable) sediment residues often makes determination of half-lives in sediment impossible in practice. Consequently, the concept of a "total system" half-life has been introduced to support this classification scheme.

The following guidance on the interpretation of OECD 308 data represents a practical approach. OECD guidelines do not provide any definitive fail/pass criteria for the OECD 308 study and there is only limited regulatory precedent for the values used in this scheme. The criteria for OECD 308 results for the different degradation phrases are shown in Table 10.

Table 10. Summary of pass criteria for degradation phrases based on OECD 308.

Pass criteria	Summary phrase
DT50 ≤ 32d for the total system.	[Name of the substance] is degraded in the environment.
DT50 ≤ 32d for the total system but >15% of parent compound remaining at the end of the study	[Name of the substance] is slowly degraded in the environment.
DT50 ≤ 120d for the total system.	[Name of the substance] is slowly degraded in the environment.
DT50>120d for the total system.	[Name of the substance] is potentially persistent.

When assigning a classification based on OECD 308 data, the following points should also be noted:

1. For purposes of this guidance document, DT50 is calculated as the time in days it takes for the amount of total parent material that can be extracted from the whole water/sediment system to reach 50 percent of the initial amount of parent material used to dose the test system. DT50 collectively represents the loss of parent from the test system due to its biological or chemical transformation, mineralization and/or irreversible binding to sediments.
2. For classification purposes, DT50 values should represent the disappearance rate of the parent molecule.
3. The total system DT50 should be calculated from the total amount of parent compound (i.e. water and sediment extractions added together) compared to the total amount applied at the start of the study. In practice, this normally means comparing the amount of radioactivity present as parent compound compared to the total amount of radioactivity applied at the start of the study.
4. As long as all reasonable efforts have been made to extract sediment residues (e.g. by using a range of extraction conditions), any remaining bound residue can be considered as not bioavailable and removed from the system for the purposes of calculating DT50's. Companies should provide brief information on the extraction methods used in order to justify this approach.
5. Normally data for two sediments are available. If, according to the above DT50 criteria, different degradation phrases would be obtained from each sediment, then the phrase "[Name of the substance] is slowly degraded in the environment" should be used. This may occur if the test result for the compound is "degraded" in one sediment and "slowly degraded" in the other, or if the result is "degraded" or "slowly degraded" in one sediment, but "potentially persistent" in the other.
6. The cut-off value DT50 ≤ 32d for disappearance of parent extracted from the total system is based on a combination of:

   a) The following text from ECHA guidance section R.7.9.5.1 (Ref. 3):

   "Rapid degradation in the aquatic environment may be demonstrated by other data than referred to using the standard assessment methods covered above. This may be data on biotic and/or abiotic degradation. Data on primary degradation can only be used where it is demonstrated that the degradation products shall not be classified as hazardous to the aquatic environment, i.e. that they do not fulfil the classification criteria. Scientific evidence must be provided that the substance is degraded in the aquatic environment to a level of >70% within a 28-day period. If first-order kinetics is assumed, which is reasonable at the low substance concentrations prevailing in most aquatic environments, the degradation rate will be relatively constant for the 28-day period. Thus, the degradation requirement will be fulfilled with an average degradation rate constant, k > 0.043 day-1 which corresponds to a degradation half-life of 16 days."

   b) The ratio of 3 for the P criterion for water and sediment (Table 12), and;

   c) Taking the mean of the water and sediment half-life to produce a total system half-life.
7. The cut-off DT50 value of 120d for disappearance of parent extracted from the total system is consistent with the typical duration of an OECD 308 study.

2.3.3. Interpretation of abiotic degradation studies

Abiotic degradation is normally determined from hydrolysis studies (OECD 111) or photodegradation studies (e.g. OECD 316). In principle, these can be used to demonstrate lack of persistence if the predicted half-life in the environment is less than the half-life required to fulfil the "P" criterion (Table 12). However, as discussed above, these are primary degradation mechanisms and hence information on the identity of major transformation products, and their expected ecotoxicity, should also be provided. If these conditions are met the phrase "[Name of the substance] is slowly degraded in the environment" should be used. If photolysis data are used, consideration should be given to the extrapolation from laboratory to Swedish environmental conditions. For substances that undergo rapid hydrolysis (half-life <40 days at environmentally relevant pH and temperatures) there should be no further biodegradation testing requirements based on the parent compound. Additional fate and effects data should be provided on the hydrolysis products where available.

For substances potentially fulfilling the EU PBT/ vPvB criteria (see section 2.5 and Table 12), further information on persistence will be required, which may involve a more detailed assessment of the potential ecotoxicity of any significant primary degradation products.

Ultimately, it is the half-life in the environment that is required to characterize the persistence of a compound. Hence a weight-of-evidence approach is invariably needed to ensure appropriate interpretation of measured and predicted degradation data, particularly where conflicting data exist. In all cases, sufficient supporting evidence should be provided in the detailed background information to justify the classification given.

2.3.4. Use of non-standard data when assessing degradation

To ensure consistency within the classification scheme, use of non-standard studies for characterizing persistence should be supported by sufficient information to allow adequate interpretation of the results. Such information could include source and concentration of inoculum, information on pre-exposure, temperature, test substance concentration, DO (dissolved oxygen), pH, analyte (e.g. parent compound or CO2), number of time points, number of replicates and test geometry.

2.4. Assessment of Bioaccumulation

The most widely accepted measure of bioaccumulation potential is the bioconcentration factor (BCF). The classification of the APIs based on their potential to bioaccumulate, is done according to the CLP regulation (Ref. 9). For classification purposes, a BCF in fish of ≥ 500 is indicative of the potential to bioconcentrate, according to CLP. In the context of PBT/vPvB assessment, the B and vB triggers are BCF=2000 and 5000 respectively (Ref. 4, Table R. 11-1). Note that the phrases do not necessarily relate to the "B" criterion in PBT/vPvB assessment according to REACH (Ref. 10).

In the absence of a measured BCF value, the bioaccumulation potential may be indicated from log K_{ow} (often referred to as log P_{ow} or log P), which describes partitioning of the neutral form of the molecule. CLP states that a log K_{ow} > 4 indicates that the substance may bioaccumulate. For complex ionic molecules it is more relevant to use log D_{ow} at pH 7 (see below) (Ref. 11), but the principle is the same. Note that whilst log D_{ow} ≥4 indicates a potential to bioaccumulate in aquatic organisms,

this does not fulfil the “B” criterion in PBT/vPvB assessment, which would normally be based on a BCF derived from a bioaccumulation study.

For bioaccumulation test results, one of the phrases listed in Table 11 should be included. For substances classified as PBT/vPvB no bioaccumulation phrase is given.

Table 11. Bioaccumulation phrases based on test results.

BCF or partition coefficient result	English phrase	Swedish phrase
BCF < 500 or log D_{ow} (at pH 7) < 4	[Name of the substance] has low potential for bioaccumulation.	[Substansnamnet] har låg potential att bioackumuleras.
BCF ≥ 500 or log D_{ow} (at pH 7) ≥ 4	[Name of the substance] has high potential for bioaccumulation.	Substansnamnet] har hög potential att bioackumuleras.

The K_{ow} is defined as the partition coefficient of the neutral form of a substance. The D_{ow} is the octanol/water distribution coefficient of all the forms (neutral and ionisable) of a substance and is the actual experimental result. For neutral molecules, D_{ow} will approximate to K_{ow}, but for ionisable molecules K_{ow} is derived by correcting by the acid dissociation constant pK_a using the relationship:

$$K_{OW} = D_{OW}(1 + 10(abs(pH - pK_a)))$$

However, log K_{ow} and log D_{ow} may both be poor predictors of bioaccumulation for large complex ionisable compounds, as the partitioning mechanism may be more complex than simple partitioning of the neutral species. Hence, use of log D_{ow} (at pH 7) is preferred for ionisable compounds, consistent with the ECHA guidance (Refs. 11 and 12), as it may better represent the actual partitioning behaviour, i.e. if log D_{ow} ≥4 at pH 7 then the summary phrase will be “[Name of the substance] has high potential for bioaccumulation”. Care should be taken when using computer-estimated log K_{ow} (ClogP) values, as many of these are based solely on the neutral molecule. If only such values are available, estimated log D_{ow} can be generated from estimated log K_{ow} using the equation above.

Where available, measured liposome/water distribution coefficients (log D_{lipw}) at pH ~7 can be used as a further substitute for bioaccumulation (Ref. 6).

Overall, it should be noted that the use of log K_{ow} relationships, or even log D_{ow}, for estimating BCFs for ionisable compounds is questionable. For example, Meylan *et al*. (Ref. 7) evaluated a large data set of both non-ionic and ionic compounds. Whilst reasonable regression equations were obtained for non-ionic compounds, no acceptable regression was obtained for ionic compounds. These data suggest that significant bioaccumulation potential is unlikely for ionisable compounds. However, the fact that no clear correlations were observed suggests that log K_{ow} may be a poor predictor of bioaccumulation potential.

In summary, for the purpose of this classification scheme, the BCF should be used to select the appropriate phrase. If no measured BCF is available, log K_{ow}, log D_{ow} or log D_{lipw} at pH 7 can be used. However, further discussion concerning the relevance of the available data, possibly referencing the work by Meylan *et al*. (Ref. 7), may be included in the detailed background information.

2.4.1. Use of non-standard data when assessing bioaccumulation

To ensure consistency within the classification scheme, use of non-standard studies for characterizing bioaccumulation should be supported by sufficient information to allow adequate interpretation of the results.

2.5. PBT/vPvB Assessment criteria

The REACH criteria for PBT/vPvB classification are given in Table 12. To be classified as PBT or vPvB, a compound must meet all the criteria given in Table 12 for "P", "B" and "T" ("T" is only applicable for PBT, not for vPvB). If the compound is not classified as PBT or vPvB, section 2.5 is not applicable.

Note that the criteria for PBT/vPvB classification in Table 12 to some extent differ from the criteria otherwise specified in this guideline to assess environmental risk, degradation and bioaccumulation.

Table 12. PBT and vPvB criteria according to REACH (Ref. 10).

	PBT criteria	vPvB criteria
P	Half-life >60 d in marine water or half-life >40 d in freshwater* or half-life >180 d in marine sediment or >120 d in freshwater sediment*	Half-life >60 d in marine water or freshwater or half-life >180 d in marine or freshwater sediment
B	BCF >2000	BCF > 5000
T**	Chronic NOEC <0.01 mg/L or CMR *** or STOT RE (cat 1 or 2) or endocrine disrupting effects (cat 1)	Not applicable

** For marine environmental risk assessment, half-life data in freshwater and freshwater sediment can be overruled by data obtained under marine conditions.*

*** In case the substance fulfils the T criterion based on classification in the CLP inventory, no additional testing is needed for the toxicity assessment.*

**** CLP-classifications: Carcinogenic (cat 1A or 1B), Mutagenic (cat 1A or 1B) or Reprotoxic (cat 1A, 1B or 2) (Ref. 4)*

Compounds that have a PEC/PNEC ratio <1, and at the same time are PBTs and/or vPvBs, shall not be labelled as posing an insignificant or low risk, but in the detailed background information the hazard information shall be indicated in accordance with Table 13 (Table 14 for Swedish).

Table 13. Summary phrases and detailed background information for PBT and vPvB (Ref. 4)

PEC/PNEC ≤ 1, fulfilling PBT/vPvB criteria		
Test result	**Summary phrases**	**Detailed background information**
PEC/PNEC ≤ 1, fulfilling PBT criteria	Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.	The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures indicate that [name of the substance] would have insignificant/low* long-term risk to the environment. However, the half-life in the environment** is >xx days, the BCF is >2000 and the chronic toxicity is <0.01 mg/L (NOEC). [Name of the substance] should therefore be regarded as a PBT substance, according to the ECHA Guidance criteria, and as such the current PEC/PNEC ratio may underestimate the potential for long-term risks to aquatic organisms.
PEC/PNEC ≤ 1, fulfilling vPvB criteria	Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.	The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures indicate that [name of the substance] would have insignificant/low* long-term risk to the environment. However, the half-life in the environment** is >xx days and the BCF is >5000. [Name of the substance] should therefore be regarded as a vPvB substance, according to the ECHA Guidance criteria, and as such the current PEC/PNEC ratio may underestimate the potential for long-term risks to aquatic organisms.

PEC/PNEC > 1, fulfilling PBT/vPvB criteria		
Test result	**Summary phrases**	**Detailed background information**
PEC/PNEC > 1, fulfilling PBT criteria	Use of the medicine has been considered to result in moderate /high* environmental risk. Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/ vPvB substance.	Use of the medicine has been considered to result in moderate/high* environmental risk. In addition, the half-life in the environment** is >xx days, the BCF is >2000 and the chronic toxicity is <0.01 mg/L (NOEC). [Name of the substance] should therefore be regarded as a PBT substance according to the ECHA Guidance criteria.
PEC/PNEC > 1, fulfilling vPvB criteria	Use of the medicine has been considered to result in moderate/high* environmental risk. Hazardous environmental properties. According to the established EU criteria, the compound should be regarded as a PBT/ vPvB substance.	Use of the medicine has been considered to result in moderate/high* environmental risk. In addition, the half-life in the environment** is >xx days and the BCF is >5000. [Name of the substance] should therefore be regarded as a vPvB substance according to the ECHA Guidance criteria.

** delete as appropriate*

*** specify environmental compartment (seawater/freshwater/sediment etc.)*

Table 14. Summary phrases and detailed background information in Swedish for PBT and vPvB (Ref. 4)

PEC/PNEC ≤ 1, fulfilling PBT/vPvB criteria		
Test result	**Summary phrases**	**Detailed background information**
PEC/PNEC ≤ 1, fulfilling PBT criteria	Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att [substansnamnet] medför försumbar/låg* risk för miljöpåverkan. Dock är halveringstiden i miljön** >xx dagar, BCF är >2000 och den kroniska toxiciteten är <0,01 mg/L (NOEC). [Substansnamnet] ska därför betraktas som en PBT-substans enligt kriterierna i ECHA:s guidance, och det är därför möjligt att den aktuella PEC/PNEC-kvoten underskattar risken för långtidseffekter på vattenlevande organismer.
PEC/PNEC ≤ 1, fulfilling vPvB criteria	Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att [substansnamnet] medför försumbar/låg* risk för miljöpåverkan. Dock är halveringstiden i miljön** >xx dagar och BCF är >5000. [Substansnamnet] ska därför betraktas som en vPvB-substans enligt kriterierna i ECHA:s guidance, och det är därför möjligt att den aktuella PEC/PNEC-kvoten underskattar risken för långtidseffekter på vattenlevande organismer.

PEC/PNEC > 1, fulfilling PBT/vPvB criteria		
Test result	**Summary phrases**	**Detailed background information**
PEC/PNEC > 1, fulfilling PBT criteria	Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Dessutom är halveringstiden i miljön**>xx dagar, BCF är >2000 och den kroniska toxiciteten är <0,01 mg/L (NOEC). [Substansnamnet] ska därför betraktas som en PBT-substans enligt kriterierna i ECHA:s guidance.
PEC/PNEC > 1, fulfilling vPvB criteria	Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Särskilt miljöfarliga egenskaper. I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Dessutom är halveringstiden i miljön** >xx dagar och BCF är >5000. [Substansnamnet] ska därför betraktas som en vPvB-substans enligt kriterierna i ECHA:s guidance.

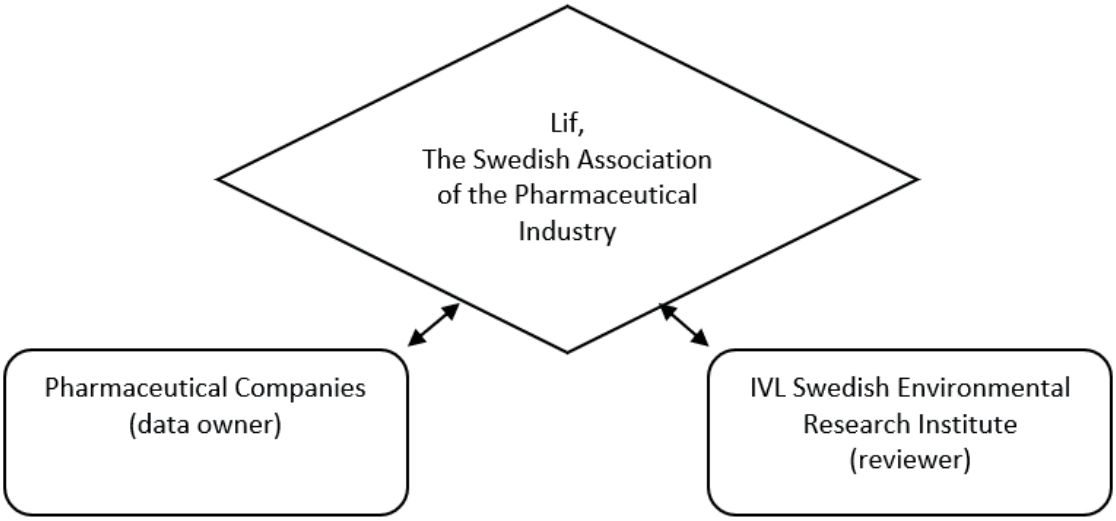
** delete as appropriate*

*** specify environmental compartment (seawater/freshwater/sediment etc.)*

3. Quality assurance process

To ensure consistent application of the guideline, an independent reviewer, IVL Swedish Environmental Research Institute, has been appointed to review the information submitted by companies (Fig. 2). The reviewer checks the data submitted and that the guideline has been followed, making recommendations for amendments where appropriate. On occasions the reviewer may request further information from the company, via Lif, if required to support the proposed classification phrases. However, it is important to note that the individual companies are ultimately responsible for the environmental summaries they publish in the Fass database.

Figure 2. Partners in the quality assurance process of environmental classification at www.fass.se.



4. References

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5. European Chemicals Agency, 2016. Guidance on information requirements and chemical safety assessment: Chapter R.16: Environmental exposure assessment: version 3.0, February 2016. https://echa.europa.eu/documents/10162/17224/information_requirements_r16_en.pdf/b9f0f406-ff5f-4315-908e-e5f83115d6af
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9. Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures. 2008 http://data.europa.eu/eli/reg/2008/1272

5. Document history

Version	Date	Changed by	Changes
1.0	2012		First version.
2.0	2021	Lif and IVL	General: LIF --> Lif and IMS Health --> IQVIA Introduction – added information regarding the update don in 2021 1 – figure 1 updated. 1.1 – update of the Swedish translation for the phrase given when environmental risk assessment may not have been undertaken. Added information regarding that even though biomolecules are exempted from environmental risk classification it should be remembered that these molecules may be biologically active. 1.4 – added information; Preferably references to original data should be presented and references to Safety Data Sheets should be avoided. The reference should include year of publication and if adequate a version number. 2 – added information; The following sections describes how to collect data. See Appendix 1 for an example of how to present data. 2.2.1 – added information; If the salt-part (the counter-ion) is subtracted from the total amount this should be explained in the document. Updated information regarding Short-term and long-term effects data for algae, crustaceans and fish. Updated number of inhabitants in Sweden (Also updated in Appendix 1) 2.2.2 – added information regarding that EC10-data can be used for long time studies. (Also updated in Appendix 1) 2.2.2.1 – added information; “if results from three trophic levels are available”. Added information regarding EC_{10}. 2.3.2 5. – clarification that only brief information is needed. 2.3.4 – clarification of the the abbreviation “DO”. 2.5 – updated text regarding REACH/PBT/vPvB Classification. 5 – document history added Appendix 1 – updated text regarding *PNEC (µg/L) = lowest EC10 or NOEC/10, where 10is the assessment factor used for three long-term ecotoxicity data endpoints. EC10 for rainbow trout has been used for this calculation since it is the most sensitive of the three tested species*
3.0	2021	Lif	*Minor update* 2.2.1 and Appendix 1 – equation updated so it matches P that was updated in version 2.0.
2025 1.0	2025	Lif and IVL	*Major update – new version of the EMA Guideline. Revision of the entire document.*

Appendix 1 – Template for environmental information at www.fass.se

[name of the substance]

Environmental risk: Use of [name of the substance] has been considered to result in *insignificant* environmental risk.

Degradation: [Name of the substance] is *slowly degraded* in the environment.

Bioaccumulation: [Name of the substance] has *low potential* for bioaccumulation.

Detailed background information

Environmental Risk Classification

Predicted Environmental Concentration (PEC)

PEC is calculated according to the following formula[1]:

$$PEC = \frac{A * 10^9 * (100 - R)}{365 * P * V * D * 100} = 1{,}37 * 10^{-6} * A * (100 - R)$$

Where:

A (total sold amount of API in Sweden year ____, information obtained from Lif) = ___ kg
R (removal rate). If default value (zero) is not used for R, please present the value and a justification in accordance with 2.2.1.1 and 2.2.1.2 in FASS Guideline (2025).

Default values:

P = number of inhabitants in Sweden = $10*10^6$
V (L/day) = volume of wastewater per capita and day = 200 (ECHA default[2])
D = factor for dilution of waste water by surface water flow = 10 (ECHA default[2])

PEC = xx µg/L

[1] The parameters used in the equation are described in table 7, page 16 in this guidance.

[2] European Chemicals Agency, 2016. Guidance on information requirements and chemical safety assessment: Chapter R.16: Environmental exposure assessment: version 3.0, February 2016.

Predicted No Effect Concentration (PNEC)

Ecotoxicological studies[3]

Algae [Latin name] (guideline e.g. OECD 201) [Reference]:

EC_{50} 72 h [endpoint] = ___ µg/L

EC_{10} or NOEC = ___ µg/L

Crustacean [Latin name]:

Acute toxicity

EC_{50} ___ h [endpoint] = ___ µg/L (guideline e.g. OECD 202) [Reference]

Chronic toxicity

EC_{10} or NOEC ___ days [endpoint] = ___ µg/L (guideline eg OECD 211) [Reference]

Fish [Latin name]:

Acute toxicity

LC_{50} ___ h [endpoint] = ___ µg/L (guideline e.g. OECD 203) [Reference]

Chronic toxicity

EC_{10} or NOEC ___ days [endpoint] = ___ µg/L (guideline e.g. OECD 210) [Reference]

Other ecotoxicity data: ___

Lowest EC_{10} or NOEC (or eg EC_{50}) = ___ µg/L

AF = ___

PNEC= (lowest EC_{10} or NOEC)/AF = ___ µg/L

Justification of chosen value for PNEC and for the assessment factor (AF) e.g.

"The assessment factor (AF) 10 is used, which is the AF used for three long-term ecotoxicity data endpoints. EC_{10} for rainbow trout has been used for this calculation since it is the most sensitive of the three tested species."

[3] If the ecotoxicological test is not standardized, please specify the test with additional relevant data (e.g. medium, temperature, exposure regime, number of replicates & test geometry)

Environmental risk classification (PEC/PNEC ratio)

PEC/PNEC = ___

Justification of chosen environmental risk phrase:

PEC/PNEC ≤ xx which justifies the phrase[4] "Use of [name of the substance] has been considered to result in insignificant/low/moderate/high environmental risk."

Degradation[5]

Biotic degradation

Ready degradability:

[Test results] e.g., ___% degradation in ___ days (guideline *e.g.* OECD 301). [Reference]

Inherent degradability:

[*Test results] e.g.* ___% degradation in ___ days (guideline *e.g.* OECD 302). [Reference]

Simulation studies:

[Test results] *e.g.* DT50 ___ in water, sediment and total system (guideline *e.g.* OECD 308). [Reference]

Abiotic degradation

Hydrolysis:

[*Test results*] *e.g.* ___% degradation in ___ days (guideline *e.g.* OECD 111). [Reference]

Photolysis:

[*Test results*] *e.g.* ___% degradation in ___ days (guideline *e.g.* OECD 316). [Reference]

Justification if R ≠0, e.g. modelling results using SimpleTreat:

Justification of chosen degradation phrase:

Example: [Name of the substance] passes the ready degradation test but is not inherently degradable, the phrase "[Name of the substance] is slowly degraded in the environment" is thus chosen.

[4] See table 1 in this guidance

[5] If the degradation test is not standardised, please specify the test with the following additional data if available; source and concentration of inoculum, information on pre-exposure, temperature, test substance concentration, DO, pH, analyte (e.g. parent compound or CO2), number of time points, number of replicates & test geometry.

Bioaccumulation

Bioconcentration factor (BCF): ___

[*Test results*] (guideline *e.g.* OECD 305). [Reference]

Partitioning coefficient:

e.g. Log D_{ow} = ___ at pH 7 (guideline *e.g.* OECD 107). [Reference]

Justification of chosen bioaccumulation phrase:

Example: Since BCF < 500, the substance has low potential for bioaccumulation.

or;

Example: Since log D_{ow} < 4 at pH 7, the substance has low potential for bioaccumulation.

Excretion (metabolism)

[Name of the substance] is excreted to ___ % as parent compound and to ___ % as metabolites. The pharmacological activity of the metabolites is not known. (Reference)

A reduction of A (total sold amount API in Sweden 20xx) in the PEC calculation based on metabolism should be justified here.

PBT/vPvB assessment

If the API fulfils the criteria for PBT and/or vPvB this should be flagged and the following phrase should be added:

According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.

References

I. ECHA, European Chemicals Agency. 2008 Guidance on information requirements and chemical safety assessment. https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

II. Study report……

Lif 202504

Lif är branschorganisationen för de forskande läkemedelsföretagen i Sverige. Vi arbetar för en högkvalitativ vård och tillgång till nya behandlingar genom att stärka den svenska Life Science-sektorn i samverkan med vårdens aktörer, politiker, tjänstemän och patientföreträdare.

The research-based pharmaceutical industry

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