Environmental classification of pharmaceuticals in www.fass.se – guidance for pharmaceutical companies

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Presentation of Environmental Information

The environmental information will be presented at three levels in www.fass.se and will be available via clicking on links included at the different levels. Please note that the information will normally be given in Swedish in www.fass.se, although English translations are available in this document for comparison. However, the Level 3 information can be given in English. The three levels will be available to all, but the main users of Level 1 are thought to be patients, who would like summary information about the environmental risk, whereas Levels 2 and 3 provide progressively more detailed information. Level 2 is directed to prescribers and the information at Level 3 is directed to people specifically interested in the environmental data available and the underlying basis of the risk assessment.

To read more about the environmental classification please visit www.fass.se/miljö or www.fass.se/environment (English version).

It is intended that this classification scheme will be reviewed on an ongoing basis, and may be subject to future refinement, based on developing scientific principles, new data and regulatory guidance.

Level 1 – Patient information

Level 1 will provide a simple aquatic environmental risk phrase, based on the PEC/PNEC ratio of the Active Pharmaceutical Ingredient (API). The PEC/PNEC ratio decides the wording of the aquatic environmental risk phrase as follows (to be given in Swedish):

- PEC/PNEC ≤ 0.1
  Use of the medicine has been considered to result in insignificant environmental risk
  In Swedish: **Användning av läkemedlet har bedömts medföra försumbar risk för miljöpåverkan**

- 0.1 < PEC/PNEC ≤ 1
  Use of the medicine has been considered to result in low environmental risk
  In Swedish: **Användning av läkemedlet har bedömts medföra låg risk för miljöpåverkan**

- 1 < PEC/PNEC ≤ 10
  Use of the medicine has been considered to result in moderate environmental risk

In Swedish: **Användning av läkemedlet har bedömts medföra medelhög risk för miljöpåverkan**

- PEC/PNEC > 10
  Use of the medicine has been considered to result in high environmental risk
  In Swedish: **Användning av läkemedlet har bedömts medföra hög risk för miljöpåverkan**

If there is not sufficient data to calculate the PEC/PNEC, either of the following two statements will be used:

- **Risk of environmental impact cannot be excluded, since no ecotoxicity data are available**
  In Swedish: **Risk för miljöpåverkan kan inte uteslutas då ekotoxikologiska data saknas**

The statement above is used when no ecotoxicity data are available.

- **Risk of environmental impact cannot be excluded, however some ecotoxicity data are available**
  In Swedish: **Tillgängliga ekotoxikologiska data utesluter inte risk för miljöpåverkan**

The statement above is used when some ecotoxicity data are available, but not enough to enable classification.

In the case where the PEC:PNEC<1 but the medicine is flagged as a potential PBT or vPvB, the risk phrase will be replaced with the phrase 'Hazardous environmental properties'. In Swedish: Miljöfarliga egenskaper.

Level 2 – Prescriber information

This level will repeat the environmental risk information given in Level 1, but will also include additional information about the environmental persistence (resistance to degradation) and bioaccumulation of the API. The following statements (in Swedish) will be used:

- Environmental risk: As Level 1
- Degradation: **The medicine is degraded in the environment**, **The medicine is slowly degraded in the environment** or **The medicine is potentially persistent**
  In Swedish: **Läkemedlet bryts ned i miljön, Läkemedlet bryts ned långsamt i miljön** or **Läkemedlet är potentiellt persistent**
- Bioaccumulation: **No significant bioaccumulation potential** or **Potential to bioaccumulate in aquatic organisms**
  In Swedish: **Läkemedlet har inte potential att lagras upp i vattenlevande organismer** or **Läkemedlet har potential att lagras upp i vattenlevande organismer**

- If the pharmaceutical fulfills the criteria for PBT (Persistent, Bioaccumulative and Toxic) and/or vPvB (very Persistent and very Bioaccumulative), the following phrase should be added: **According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance.**
  In Swedish: **I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans**

If there is insufficient data to characterize the potential for degradation, the following statement will be used:

- **The potential for persistence cannot be excluded due to lack of data**
  In Swedish: **Det kan inte uteslutas att läkemedlet är persistent, då data saknas**

If there is insufficient data to characterize the potential for bioaccumulation, the following statement will be used:

- **The potential for bioaccumulation cannot be excluded due to lack of data**
  In Swedish: **Det kan inte uteslutas att läkemedlet kan bioackumuleras, då data saknas**

Level 3 – Specialist information

This level contains detailed environmental information. Please provide the following data (in Swedish or English):

- Risk assessment, i.e. PEC/PNEC, calculations as well as the specific PEC and PNEC calculation, given in µg/L, where applicable
- Total sold amount in kilograms of API on the Swedish market (including all products and enantiomers containing the same API) in the most recent year for which data are available. This figure will be provided by the Swedish Association of the Pharmaceutical Industry, LIF, and is based on statistics from the Swedish system Läkemedelsstatistik (LS)

Where applicable, please also include the following information:

- Results from ecotoxicity tests (given in µg/L). Please provide the species names both in Swedish and in Latin
- Results from degradation tests (biotic and abiotic)
- Partition coefficient (e.g. octanol/water, log K_{ow}, log D or logDlipw or other indicator of bioaccumulation if more appropriate)
- Test guidelines used (e.g. OECD, FDA)
- Information about which forms the pharmaceutical is excreted as, parent compound as well as metabolites, and the percentages thereof
- Results of CMR (Carcinogenic, Mutagenic, Reprotoxic) tests and statement on endocrine disrupting potential
- Pharmacological activity of the human metabolites
- Data interpretation in the context of risk and hazard assessment

Please note that according to Swedish standard, you should use comma as decimal point e.g. 2,3 and not 2.3.

Exemptions (in accordance with the EU EMEA guideline for environmental risk assessment of pharmaceuticals (Ref. 1))

According to the EU EMEA Environmental Risk Assessment guideline, vitamins, electrolytes, amino acids, peptides, proteins, 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.

Therefore, no environmental information will normally be provided for these pharmaceuticals, and they will be marked at all levels with the following text:

- **Use of xx has been considered to result in insignificant environmental impact**
  In Swedish: **Användning av xx bedöms inte medföra någon miljöpåverkan**

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

How to assess environmental risk and hazard

Data Collection

The following information, where available, should be used when classifying the APIs in accordance with the environmental information system:

- Sales data in kilograms of API in Sweden: For marketed products, data from the most recent year should be obtained from LIF. For newly introduced products (on patent), it is recommended to use the forecasted sales five years after launch when calculating the environmental risk
- 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 a sewage treatment plant
  - 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
- Biodegradation: Ready biodegradability and/or other relevant biodegradation studies
- Abiotic degradation: photolysis, hydrolysis, volatilisation
- 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.
- Log K_{ow} (or log D_{ow} or logDlipw if appropriate), or the bioconcentration factor (BCF)

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 preparations, each active ingredient should be assessed. It is preferred to use experimental data rather than estimated data (e.g. measured ecotoxicity/K_{ow} vs QSAR). If estimated 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. All data should, where possible, be supported by the appropriate OECD, FDA or similar guidelines. Table 1 shows some comparable test guidelines.

Table 1. Some comparable OECD and FDA test guidelines

Test	**OECD guideline**	**FDA guideline**
Algal growth inhibition	201	4.01
Daphnia 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

Data sharing

A mechanism for data sharing, review and publication within www.fass.se is available e.g. for generic compounds (i.e. if a company has taken the lead responsibility for compiling the environmental data and undertaking the classification). Companies lacking environmental data for the APIs, will be able to link to the environmental information produced by another company. In that case the following text will automatically appear below the headline "Environmental impact/Miljöpåverkan":

- **Environmental information for (substance name) originates from (name of the company) for (product name)**
  In Swedish: **Miljöinformation för (substansnamn) är framtagen av (företagsnamn) för (produktnamn)**

References

The environmental test results, together with the test guidelines followed, should be stated (OECD, FDA etc.). 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.

References, internal or external, should be given in association with all the submitted data. Companies are recommended to take external data into account for the evaluation of the environmental risk and hazard of the API.

Environmental Risk Assessment (ERA)

In order to assess the environmental risk of an API, the Predicted Environmental Concentration (PEC) and the Predicted No Effect Concentration (PNEC) need to be calculated.

Predicted Environmental Concentration (PEC)

The PEC is obtained by using the following formula, and follows the basic principles of the EMEA ERA 2002 draft guidance (Ref. 2):

$$PEC\ (\mu g/L) = \frac{A \times 1000000000 \times (100-R)}{365 \times P \times V \times D \times 100} \qquad \textit{Equation 1}$$

$$= 1.5 \times 10^{-6} \times A \times (100-R) \qquad \textit{Equation 2}$$

where:

A (kg/year) = total actual API sales (active moiety) in Sweden for the most recent year. The sales data will be obtained from LIF, and should include all products containing the same API as well as enantiomers of the API. All salts of the API should be taken into account (e.g. metoprolol succinate and metoprolol tartrate). The 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. 3). 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.

R (%) = removal rate (due to loss by adsorption to sludge particles, by volatilization, hydrolysis or biodegradation) = 0 if no data is available. 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 TGD (Ref. 4), Part II, Chapter 3, Appendix II). It is recommended to use SimpleTreat, but alternative models may be used if reasonably justified. To ensure consistency within the classification scheme, use of non-standard studies should be supported by sufficient information to allow adequate interpretation of the results. Such information should include source & concentration of inoculum, information on pre-exposure, temperature, test substance concentration, DO, pH, analyte (e.g. parent compound or CO_2), number of timepoints, number of replicates & test geometry. If an OECD 308 study is available and demonstrates >60% mineralization (or 90% primary degradation) by the end of the 100d test period, it is considered reasonable to

assume that the substance would be readily removed in a sewage treatment plant (equivalent to passing the Ready biodegradation test but failing the '10d window').

P = number of inhabitants in Sweden = 9×10^6

V (l/day) = volume of wastewater per capita and day = 200 (TGD default)

D = factor for dilution of waste water by surface water flow = 10 (TGD default)

[Note; the factor of 1000000000 in Equation 1 converts the quantity used from kg to µg. The factor of 365 in the denominator converts from annual to daily quantity used. Simplifying all the default values into a single factor gives Equation 2]

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. On Level 3, however, it is still expected to find both the MEC and PEC figures to enable comparison.

Predicted No Effect Concentration (PNEC)

The PNEC should preferably be obtained by applying assessment factors to long-term ecotoxicity data in accordance with the TGD (Ref. 4 – see Part 2, Chapter 3.3, Table 16). If long-term data is lacking, short-term ecotoxicity data may be used. An assessment factor of 1000 is normally applied to the most sensitive of three short-term toxicity (LC/EC_{50}) endpoints. However, the assessment factor may be reduced to 100, 50 or 10, depending on the number of long-term NOEC endpoints available, providing long-term data are available for the species with the lowest acute LC/EC_{50} (see TGD, p101, Table 16).

The assessment factors recommended in the TGD may not always be applicable, e.g. if particular 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 assessment factor would be more appropriate. This needs to be considered on a case-by-case basis, with justification provided for the assessment factor used.

Ideally, ecotoxicological data should be provided for three trophic levels (usually fish, *Daphnia* and algae). However, 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.

If a valid PNEC cannot be calculated, the Level 1 phrases; 'Risk of environmental impact cannot be excluded, since no ecotoxicity data are available' or 'Risk of environmental impact cannot be excluded, however some ecotoxicity data are available' should be used.

PEC/PNEC ratio

The environmental risk is estimated by calculating the PEC/PNEC ratio. This defines the appropriate risk phrase to be used in Levels 1 and 2 of the classification scheme.

Consideration of hazardous environmental properties

Persistence

- Persistence is characterized by the potential for a substance to resist degradation in the environment. Degradation mechanisms may be either biotic (biodegradation) or abiotic.

Interpretation of biodegradation studies

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).

If a substance passes the criteria for 'ready' biodegradability, as defined in the OECD 301 test guideline series (or equivalent), the level 2 phrase 'The medicine is degraded in the environment' should be used. If a substance passes the criteria for 'inherent' biodegradability, as defined in the TGD (see below), the level 2 phrase 'The medicine is slowly degraded in the environment' should be used. If a substance fails to pass the criteria for 'ready' or 'inherent' biodegradability and there are no simulation studies or analytical monitoring data to support elimination within the TGD half-lives, the level 2 phrase 'The medicine is potentially persistent' should be used.

Note that the level 2 phrase here does not necessarily relate to the 'P' criteria in PBT/vPvB assessment, unless the underlying data are based on a higher tier study such as the OECD 308.

If 'inherent' biodegradation tests (OECD 302B or OECD 302C) are used to demonstrate non-persistence, according to the TGD the following criteria should be met (see TGD Section 4.4.3.3):

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

Whilst ultimate mineralisation is ideal, data showing primary degradation based on specific analysis of the test compound could also be considered, since it relates to loss of pharmacological activity of the parent compound. However, in such cases, information to demonstrate the expected reduction in ecotoxicity should also be provided. This might be based on direct measurement or, if the identity of the transformation products is known, on a comparison with human metabolites and relative pharmacological activity, for example.

Interpretation of abiotic degradation studies

Abiotic degradation is normally determined from hydrolysis studies (OECD 111) or photodegradation studies (eg OECD draft guideline). 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' criteria (see Table 2). 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 photolysis data are used, consideration should be given to the extrapolation from laboratory to Swedish environmental conditions.

To ensure consistency within the classification scheme, use of non-standard studies for characterising persistence should be supported by sufficient information to allow adequate interpretation of the results. Such information should include source & concentration of inoculum, information on pre-exposure, temperature, test substance concentration, DO, pH, analyte (e.g. parent compound or CO_2), number of timepoints, number of replicates & test geometry.

For substances potentially fulfilling the EU PBT/ vPvB criteria, 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 in order to characterize the persistence of a compound. Hence a 'weight-of-evidence' approach is invariably needed in order to ensure appropriate interpretation of measured and predicted degradation data, particularly where conflicting data exist. In all cases, sufficient supporting evidence should be provided at Level 3 in order to justify the classification given.

Bioaccumulation

The most widely accepted measure of bioaccumulation potential is the Bioconcentration Factor (BCF). In the context of PBT/vPvB assessment in the TGD (Ref. 4) the B and vB triggers are BCF=2000 and 5000 respectively (Table 2).

In the absence of a measured BCF value, the bioaccumulation potential may be indicated from log $K_{ow.}$ The TGD states that a log K_{ow} >3 indicates that the substance may bioaccumulate. For complex ionic molecules it is more relevant to use log D_{ow} at pH 7, but the principle is the same. Hence, one of the following phrases should be included at Level 2:

If log D_{ow} (at pH 7) < 3 '**No significant bioaccumulation potential**'
In Swedish: **Läkemedlet har inte potential att lagras upp i vattenlevande organismer**
If log D_{ow} (at pH 7) ≥ 3 '**Potential to bioaccumulate in aquatic organisms**'
In Swedish: **Läkemedlet har potential att lagras upp i vattenlevande organismer**

Note that whilst log D_{ow} >3 indicates a potential to bioaccumulate in aquatic organisms, this does not fulfill the 'B' criteria in PBT/vPvB assessment, which would normally be based on a BCF derived from a bioaccumulation study.

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 pKa using the relationship $K_{ow}=D_{ow}(1+10(abs(pH-pKa)))$ (equation 1). 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, as it may better represent the actual partitioning behavior, ie if log D_{ow} >3 at pH 7 then the level 2 phrase will be 'Potential to bioaccumulate in aquatic organisms'. 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 equation 1 above.

Where available, measured liposome/water distribution coefficients (logDlipw) at pH ~7 can be used as a further substitute for bioaccumulation (Ref. 5).

Overall, it should be noted that the use of log K_{ow} relationships, or even log $D_{ow,}$ for estimating bioconcentration factors (BCF) for ionisable compounds is questionable. For example, Meylan *et al*. (Ref. 6) evaluated a large data 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 (see Figures 1 and 2, courtesy of SETAC Press).

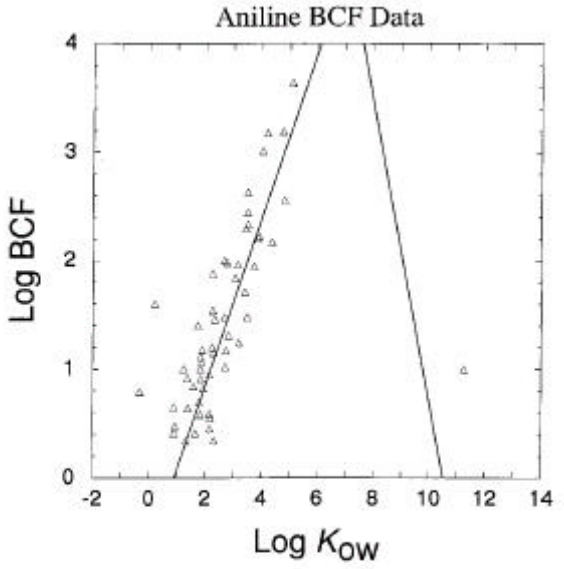

Fig. 4. Measured log BCF versus log K_{ow} for 56 anilines. The solid lines represent the two linear equations used by the new method for nonionics in the log K_{ow} ranges of 1 to 7 and >7.

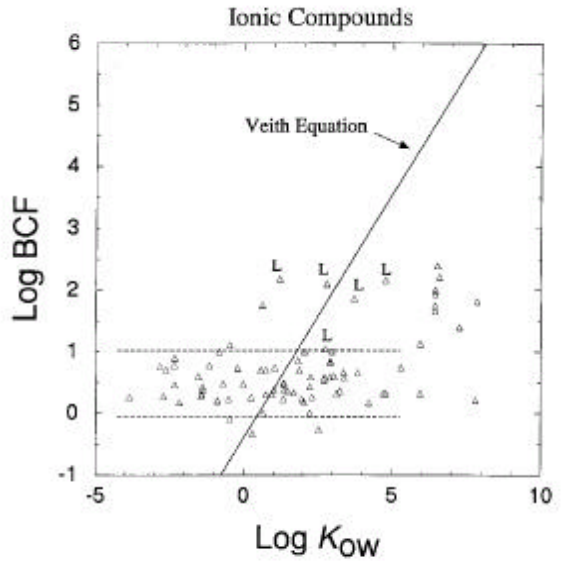

Fig. 5. Measured log BCF versus log K_{ow} for 84 ionic compounds. The solid line represents the equation of Veith and Kosian [14]. Points marked **L** represent compounds with long (≥11 carbons) alkyl chains; the dashed lines show that most compounds have log BCF values between 0 and 1.

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 log D_{ow} or log Dlipw at pH 7 should be used to select the appropriate level 2 phrase. However, further discussion concerning the relevance of the available data, possibly referencing the work by Meylan *et. al*. (Ref. 6), may be included in Level 3.

PBT/vPvB Assessment criteria

The TGD criteria for PBT/vPvB Classification are given in Table 2. For the purpose of this classification scheme, and where relevant data are available, any compound meeting the criteria given in Table 2 will be flagged as a PBT or vPvB, as appropriate. Note that all three properties, ie 'P', 'B' and 'T' are required in order to classify as 'PBT'.

Table 2. PBT and vPvB criteria according to TGD

Criterion	PBT-criteria	vPvB-criteria
P	Half-life >60 d in marine water or >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 endocrine disrupting effects.	Not applicable.

* For the purpose of marine environmental risk assessment, half-life data in freshwater and freshwater sediment can be overruled by data obtained under marine conditions.
** Carcinogenic, Mutagenic or Reprotoxic

With regard to the compounds that have a PEC/PNEC ratio <1, and at the same time are PBTs and/or vPvBs, these would not be labeled as posing an insignificant or low risk on Level 1, but rather refer to the hazard information on Level 3 in accordance with Table 3.

Table 3. Risk and hazard phrases at Level 1, 2 and 3 for compounds with PBT and/or vPvB properties

PEC:PNEC £ 1 , fulfilling PBT/vPvB criteria		
Level 1	**Level 2**	**Level 3**
Hazardous environmental properties In Swedish: Miljöfarliga egenskaper	According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. In Swedish: I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures would indicate that "Compound A" 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). "Compound A" should therefore be regarded as a PBT substance, according to the EU TGD 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		
Level 1	**Level 2**	**Level 3**
		In Swedish: Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att ”Ämne A” 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). ”Ämne A” ska därför betraktas som en PBT-substans enligt EU TGD:s kriterier, och det är därför möjligt att den aktuella PEC/PNEC-kvoten underskattar risken för långtidseffekter på vattenlevande organismer. Or: The calculated PEC/PNEC ratio is ≤ 1. Hence, risk assessment procedures would indicate that “Compound A” 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. “Compound A” should therefore be regarded as a vPvB substance, according to the EU TGD criteria, and as such the current PEC/PNEC ratio may underestimate the potential for long-term risks to aquatic organisms. In Swedish: Den beräknade PEC/PNEC-kvoten är ≤ 1. Denna kvot indikerar normalt att ”Ämne A” medför försumbar/låg* risk för miljöpåverkan. Dock är halveringstiden i miljön** >xx dagar och BCF är >5000. ”Ämne A” ska därför betraktas som en vPvB-substans enligt EU TGD:s kriterier för vPvB-klassificering, 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		
Level 1	**Level 2**	**Level 3**
Use of the medicine has been considered to result in moderate/high* environmental risk. <u>Hazardous environmental properties</u> In Swedish: Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. <u>Miljöfarliga egenskaper</u>	According to the established EU criteria, the compound should be regarded as a PBT/vPvB substance. In Swedish: I enlighet med EU:s fastställda kriterier ska substansen betraktas som en PBT/vPvB-substans.	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). "Compound A" should therefore be regarded as a PBT substance according to the EU TGD criteria. In Swedish: 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). "Ämne A" ska därför betraktas som en PBT-substans enligt EU TGD:s kriterier. Or: 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. "Compound A" should therefore be regarded as a vPvB substance according to the EU TGD criteria. In Swedish: Användning av läkemedlet har bedömts medföra medelhög/hög* risk för miljöpåverkan. Dessutom är halveringstiden i miljön** >xx dagar och BCF är >5000. "Ämne A" ska därför betraktas som en vPvB-substans enligt EU TGD:s kriterier.

* delete as appropriate

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

References

1. Committee for Medicinal Products for Human Use (CHMP); Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. 1 June 2006, Ref EMEA/CPMP/SWP/4447/00.

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