EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 October 2014
EMA/CVMP/ERA/52740/2012
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on the assessment of persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances in veterinary medicinal products

Draft

Draft agreed by Environmental Risk Assessment Working Party (ERAWP)	31 May 2012
Adopted by CVMP for release for consultation	12 July 2012
Start of public consultation	25 July 2012
End of consultation (deadline for comments)	1 February 2013
Agreed by ERAWP	September 2014
Adopted by CVMP for release for second consultation	9 October 2014
Start of second public consultation	27 October 2014
End of second consultation (deadline for comments)	27 January 2015

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Introduction

Persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substances, are substances of very high concern because of their persistence, their ability to accumulate in living organisms and their toxicity. Due to the combination of these intrinsic properties, they can pose serious concerns for the environment.

The requirement to perform a PBT/vPvB screening for veterinary medicinal products (VMPs) is specified in the current CVMP guideline on 'Environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38' (EMEA/CVMP/ERA/418282/2005-Rev.1). In the CVMP guideline it is stated that the cut-off values for each of these criteria (persistence, toxicity and bioaccumulation) are given in the EU technical guidance document (EU TGD, 2003) for industrial chemicals and biocides. However, no further guidance is given on how to perform a PBT assessment for VMPs. Moreover, the EU technical guidance document referred to is no longer in use and the legal framework under which it was written has been replaced by new legislation, in particular the new legislation on chemicals and supporting guidance (Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)).

Annex XIII of Regulation (EC) No 1907/2006 (as amended by Regulation (EC) 253/2011) lays down the criteria for the identification of PBT/vPvB substances, and together with the supporting technical guidance are used as a point of reference for the assessment of the PBT/vPvB of a substance/product within different legislative frameworks in the EU (e.g, for pesticides or biocides), and serve as harmonised criteria.

Scope

This guideline is intended to provide guidance on how PBT/vPvB substances are screened and assessed in accordance with Annex XIII of Regulation (EC) No 1907/2006 and its guideline documents (ECHA 2012a-d), with focus on the scientific data/information, parameters and default values that should be used for the assessment. This guideline has been developed taking into account, in particular, which scientific data/information is expected to be available for the VMPs for which a PBT/vPvB screening will be required.

This guideline also addresses general principles on how VMPs containing a substance that has been identified as PBT should be further assessed, within the context of the environmental risk assessment and benefit-risk assessment of the product concerned.

PART 1. IDENTIFICATION OF PBT/VPVB SUBSTANCES

1. General considerations regarding the identification of potential PBT or vPvB substances contained in VMPs

PBT/vPvB substances are substances which will bioaccumulate in organisms and persist in the environment. Due to their physico-chemical characteristics, it is neither possible to predict the environmental fate of these substances nor the kind of adverse effects that could occur over long periods of time. The concern is that even if the emission of such a substance into the environment is stopped, this may not necessarily result in a reduced concentration of the substance in the environment and, subsequently, in biota. Chronic exposure and long term and cumulative adverse effects may lead to uncertainty when calculating the predicted environmental concentration (PEC) via established exposure models, and/or establishing the predicted no effect level (PNEC) from standard laboratory tests.

Within the authorisation procedure for VMPs, an environmental risk assessment (ERA) is required to assess the potential for VMPs to affect non-target species in the environment, including both aquatic and terrestrial species.

The ERA is performed according to the VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) guideline GL 6: Environmental impact assessment (EIAs) for veterinary medicinal products (VMPs) – Phase I (CVMP/VICH/592/1998), (VICH 2000), the CVMP/VICH guideline GL 38 on environmental impact assessment for veterinary medicinal products - Phase II (CVMP/VICH/790/03-FINAL) (CVMP/VICH 2005), and the guideline on environmental impact assessment for veterinary medicinal products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1) (CVMP 2008).

The ERA is based on the accepted principle that risk is a product of the exposure, fate and effects assessments of the VMP for the environmental compartments of concern. The Phase II ERA is based on a RQ approach, which is the ratio of the predicted environmental concentration (PEC) and the predicted no effect concentration (PNEC) on non-target organisms. The RQ (PEC/PNEC) is compared against a value of 1, and a value less than 1 indicates that no further testing is recommended. If this assessment results in a possible risk to the environment (RQ>1), several steps can be taken to refine the risk assessment. If an unacceptable risk is identified at the end of the assessment, appropriate mitigation measures should be proposed in order to reduce the risk to an acceptable level.

For the assessment of PBT/vPvB, it is very difficult to predict fate and environmental concentrations, and thus bioaccumulation and effects of PBT/vPvB substance in the environment. Therefore, in addition to the required quantitative environmental risk assessment as describe above, it is also necessary to conduct a hazard based PBT/vPvB assessment which focuses on intrinsic properties of substances only.

Annex XIII of the REACH regulation (Regulation (EC) No 1907/2006) lays down the criteria for the identification of PBT and vPvB substances. To ensure a harmonised approach, these criteria together with the methodology in the current REACH guidance on PBT-assessment (Guidance on information requirements and chemical safety assessment Chapter R.11: PBT Assessment and

Chapters R7.a, 7.b, and R7.c on endpoints specific guidance) should be followed. The REACH guidance documents can be obtained from the ECHA website[1].

1.2. Identification of PBT/vPvB properties

The CVMP guideline in support of the VICH guidelines (EMEA/CVMP/ERA/418282/2005-Rev.1), introduces the concept of screening individual substances for PBT properties. As the Phase I assessment does not require any specific environmental data the PBT screening can only be conducted as part of the Phase II assessment. However, there are provisions as set out as in the last paragraph of the introduction of VICH GL 6, that allows further assessment of environmental risk if there are particular concerns over the activity and use of the product or active substance (the so called 'however clause'). Therefore, where a competent authority has evidence, or strong suspicion that an active substance of a product that would otherwise stop in phase I potentially has PBT/vPvB properties, a PBT/vPvB assessment could be required. For example this could be the case for substances with a valid octanol/water coefficient K_{ow} ≥4 or that has been assessed as PBT/vPvB in other regulatory frameworks. A PBT/vPvB assessment should not be requested for products for non-food producing species, for products containing natural substances, or if the substance is shown to be extensively metabolized in the animal, as defined in the Phase I decision tree.

The objective of the PBT/vPvB assessment is to determine if the substance fulfills the criteria (specified in REACH Annex XIII) for persistence, bioaccumulation and toxicity. As a starting point the assessment will be based on all the relevant data available, regardless of the compartment in which they have been derived.

As the emission to the environment will be different for VMPs for use in terrestrial animals and those for use in aquaculture, a differentiation is made in the assessment strategy.

Table 1 provides an overview of the criteria for the identification of PBT or vPvB substances, as outlined in Annex XIII of Regulation (EC) 1907/2006. As explained in the relevant REACH guidance (ECHA, 2012d), two sets of criteria exist, one for PBT substances and a second for vPvB substances. The second set was developed with the understanding that for substances that are very persistent and very bioaccumulative, high but unpredictable levels may be reached in wildlife and/or humans over extended time periods. For such substances, it is not necessary to demonstrate toxicity in laboratory testing as long-term effects can be anticipated.

[1] http://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment

144 **Table 1: PBT and vPvB criteria (taken from table R. 11-1 in ECHA (2012d): Guidance on information**
145 **requirements and chemical safety assessment Chapter R.11: PBT Assessment).**

Property	PBT-criteria	vPvB-criteria
Persistence The assessment of the persistency in the environment shall be based on available half-life data collected under the adequate conditions, which shall be described by the registrant.	- $T_{1/2}$* > 60 days in marine water, or - $T_{1/2}$ > 40 days in fresh- or estuarine water, or - $T_{1/2}$ > 180 days in marine sediment, or - $T_{1/2}$ > 120 days in fresh- or estuarine sediment, or - $T_{1/2}$ > 120 days in soil.	- $T_{1/2}$ > 60 days in marine, fresh- or estuarine water, or - $T_{1/2}$ > 180 days in marine, fresh- or estuarine sediment, or - $T_{1/2}$ > 180 days in soil.
Bioaccumulation The assessment of bioaccumulation shall be based on measured data on bioconcentration in aquatic species. Data from freshwater as well as marine water species can be used.	BCF > 2000 L/kg	BCF > 5000 L/kg
Toxicity	- NOEC/EC_{10} (long-term) <0.01mg/L for marine or freshwater organisms, or substance meets the criteria for classification as carcinogenic (category 1A[2] or 1B[3]), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A[4], 1B[5] or 2[6]) according to Regulation EC No 1272/2008** or there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to Regulation EC No 1272/2008.	Not applicable

*$T_{1/2}$ is the degradation half-life.

** Regulation on classification, labelling and packaging (CLP-Regulation (EC) No 1272/2008)

[2] *Substances known to have carcinogenic potential for humans (*epidemiological and/or animal data*)*
[3] *Substances presumed to have carcinogenic potential for humans (*animal studies)
[4] *Known human reproductive toxicant* (human evidence)
[5] *Presumed human reproductive toxicant* (animal studies)
[6] *Suspected human reproductive toxicant* (some evidence from humans or experimental animals, not sufficiently convincing to place the substance in category 1)

1.2.1. Persistence

1.2.1.1. Assessment of persistence in the soil compartment

The persistence of a substance is a key parameter to predict the potential for long-term exposure of organisms, as well as the potential for the substance to reach the aquatic environments and to be transported to distant geographical areas. It is expected that VMPs for use in terrestrial species will primarily enter the environment via spreading of manure onto agricultural land, or via direct excretion by animals on pasture. The VICH GL 38 requires an aerobic and anaerobic transformation study in soil (according to OECD guideline 307), to investigate the rate of degradation of the active substance(s) and all relevant transformation products. Persistent substances can also reach the water phase by run off or direct entry. Therefore, if besides ERA Phase II typical tier A studies on degradation studies on soil, additional information on degradation half-lives for sediment or total water/sediment system are available in the dossier, these are also relevant for PBT assessment of VMPs for use in terrestrial species. In line with REACH Annex XIII, the P criterion is considered to be fulfilled if it is met for any of the compartments (soil, sediment, water or total water/sediment system).

Persistence studies should reflect environmental temperatures in Europe and therefore preferably be conducted at 12°C, as this is the temperature established as the average EU outdoor temperature according to the EC technical guidance document on risk assessment (EC, 2003). If studies are conducted at different temperatures, extrapolation of degradation half-lives to 12°C should be considered.

The following Arrhenius equation can be used to extrapolate the degradation half-life from e.g. 20°C to 12°C:

$$DT_{50T1} = DT_{50T2} \exp\left(\frac{E_a}{R} \left(\frac{1}{T_1} - \frac{1}{T_2} \right) \right)$$

Where DT_{50T1} and DT_{50T2} are the half-lives at temperatures T_1 and T_2, respectively, E_a is activation energy (kJ mol^{-1}) and R is the gas constant (0.008314 kJ K^{-1} mol^{-1}). As long as no specific guidance on default values is given in the REACH guidance, the default value for Ea (activation energy) should be 65.4 kJ/mol[7], as specified in the EFSA guidance for use in FOCUS (EFSA, 2007).

To determine degradation rates (instead of dissipation rates) the formation of bound residues should not be confused with degradation. Degradation studies should be preferably performed with radio-labelled compounds and using the best possible extraction methods, although it could be possible to produce acceptable degradation data using an unlabelled test substance. The highest degradation half-life from the OECD 307 test should be used for the PBT assessment, until further guidance on evaluation of simulation test data on biodegradation is provided by REACH.

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

1.2.1.2. Assessment of persistence in the aquatic compartment

For VMPs that are intended for use in aquaculture, persistence in the water/sediment system is considered most relevant. The VICH GL 38 requires an aerobic and anaerobic transformation study in aquatic sediment systems (according to OECD guideline 308), to investigate behaviour and degradation rate of the active substance(s) and all relevant transformation products that are used in aquaculture systems. The water/sediment simulation studies will provide half-lives in the water phase, the sediment phase and in the total system.

For most persistent substances, removal from the aqueous phase is determined by dissipation due to partitioning to sediment rather than by true degradation. For this reason, degradation half-lives for the total system and sediment are considered most relevant to determine the degradation half-life of a substance in the aquatic environment. Thus, half-lives in water only should not be used for the assessment of persistence. However, the P criterion is considered to be fulfilled if it is met for any of the compartments (sediment, water or whole system).

A temperature extrapolation to the average EU outdoor temperature of 12°C should be applied for surface water and sediment, in a similar way to the soil compartment (see section 2.1.1). For marine water, an extrapolation to 9°C should be applied.

For VMPs used in the marine environment, the VICH GL 38 recommends carrying out the degradation study for the aquatic system under saltwater conditions (for instance according to OECD GL 308), including all aspects as mentioned above for freshwater.

1.2.2. Bioaccumulation

In accordance with the VICH guidance a log $K_{OW} \geq 4$ is used as a criterion for an assessment of bioaccumulation. When this criterion is met, evidence from metabolism/residues/excretion studies and molecular mass should be considered to see whether there is the potential for bioaccumulation to occur. If a potential for bioaccumulation is established, or if there is not sufficient data to conclude that the substance will not bioaccumulate, then a bioaccumulation study in fish (in accordance with OECD guideline 305) should be performed. However, it should be noted that a lack of accumulation in mammals does not automatically exclude a potential for accumulation in fish and other aquatic species. Reasons for this are decreased activity of enzymes involved in the transformation of xenobiotics in fish and/or lower trophic levels and other factors such as different exposure routes (e.g. via gills), differences in metabolism, different excretion routes, etc.

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

1.2.3. Toxicity

For animal welfare reasons it is recommended that the evaluation of persistence and bioaccumulation is carried out first. When the criteria for persistence and/or bioaccumulation are not met, there is no requirement to carry out evaluation of the T criterion.

A substance is considered to potentially meet the criteria for T when an acute E(L)C50 value from a standard (acute *Daphnia* and fish studies) E(L)C50 toxicity test is less than 0.1 mg/l. The T criterion for PBT assessment cannot be concluded on the basis of acute studies alone. If the above

criteria is met (screening criterion), the substance is referred to definitive T testing and chronic studies are required to confirm that the substance is indeed T (unless the E(L)C50 < 0.01 mg/l, when the substance can be concluded to be T). Normally, and for welfare considerations, the testing order for conclusion on T based on chronic data is Daphnia and then fish. If the T-criterion is fulfilled (Table 1) by the chronic algae or *Daphnia* data, a chronic fish test is not necessary. If further aquatic toxicity other than the available studies is considered necessary to conclude on the T criteria, and if there are indications that representative species from one taxonomic group are more sensitive than species from other taxonomic groups, this sensitive group should be chosen for chronic testing.

It can be assumed that for VMPs for which a Phase II assessment is necessary, information on carcinogenicity, mutagenicity, reproductive and chronic toxicity for mammals is available in other parts of the dossier. This information can also be found in MRL summary report.

PART 2. ASSESSMENT OF PRODUCTS CONTAINING A PBT SUBSTANCE

vPvB substances are resistant to environmental degradation and consequently they have been known to persist in the environment, transport long distances, bioaccumulate in human and in animal tissue, and bioconcentrate. Thus, given the potential significant impacts on human health and the environment it seems unlikely that an authorisation for a vPvB substance in a veterinary medicinal product where the substance will be released to the environment could be granted. Therefore, Part II of this guideline is based on the assessment of VMPs containing PBT substances only, with no reference to vPvBs.

2.1. Emission assessment

The terms persistent, bioaccumulative and toxic (PBT) refer to substances of very high concern for the environment because of their persistence, their ability to accumulate in living organisms and their toxicity. Carrying out an environmental risk assessment for veterinary medicinal products containing (potential) PBT substances poses challenges in relation to the technical methodology, for the emission as well as the effects assessment. A long term and cumulative adverse effects lead to uncertainty when calculating environmental concentration (PEC) via established exposure models and/or establishing the predicted no effect level (PNEC) from standard laboratory tests. Hence, the standard approach where a risk is characterised calculating the PEC/PNEC ratio to determine the risk quotient, is not well suited for products containing a substance with PBT properties.

For such products the risk characterisation will be different because of the intrinsic properties of a PBT substance, and the actual or expected emission scenarios. It will be necessary to consider knowledge on the aspects of the specific product and its use that contribute to the actual emission in the environment, e.g. application route (injection/oral/topical treatment), husbandry conditions (indoor/outdoor/confined), terrestrial/aquaculture, closed/open water systems, individual animal treatment/flock treatment, confinement of the VMP during use, control of environmental release, waste management, metabolism in the target animal, etc.

An applicant for a product containing a PBT substance should explore all possibilities regarding emissions of the product in order to allow for a tailor-made assessment of the PBT- containing product. All relevant exposure scenario(s) should be used to obtain emission estimations. Calculations of the (maximum) entry load or emission into the environment should be made initially followed by more refined calculations, if necessary, and where suitable data are available. Robust metabolism data from the dossier could be used to refine the environmental emission scenarios, e.g. if the PBT substance is extensively metabolised (see definition in VICH guideline GL6) or if metabolites can be shown to no longer fulfil the PBT criteria.

Documented knowledge of the product and its potential uses could allow refinement of scenarios, e.g. if certain default values are clearly out of scope for the specific VMP (refer to VICH GL 6),

Where experimental data are available, in general these data should take precedence over models and predictions.

Generally, the risk characterisation for the environment considers predicted or actual emissions to estimate the incidence or severity of potential adverse effects likely to occur in environmental

compartments. Given that characterising the risk to specific environmental compartments by deriving the PEC/PNEC ratio is not possible for PBT substances, a qualitative evaluation of the likelihood that an effect is occurring under specific conditions of exposure or will occur under the expected conditions of exposure is then needed. Therefore, if the release is controlled and the environmental compartment is not exposed, the PBT assessment can stop here. If concerns remain, further information/testing (e.g., other knowledge of the substance/ product concerned, e.g. any knowledge about pharmacokinetics or metabolism of the active substance known from other parts of the dossier, should be taken into consideration to come to more firm conclusions regarding the true ability for persistence or bioaccumulation) may be needed to refine the classification of the substance, or determine additional risk mitigation measures that would effectively lower environmental exposure.

The outcome of the assessment emission scenario should clarify the potential for an environmental impact, the need for further studies where indispensable data are missing or inconclusive, and the need for risk management measures for the product.

2.2. Risk Management

PBT substances pose concerns in the environment due to their intrinsic problematic properties. However, in veterinary medicine some pathogens are difficult to treat, and long-lasting, toxic compounds may be necessary to combat the disease for the animal. Therefore, competent authorities should not base their risk management decisions solely on hazard based PBT classification, but explore all available knowledge.

The purpose of risk management is to control and limit the environmental emission as much as possible for PBT substances, for example by limiting certain uses of the product, using different application methods, by setting appropriate risk mitigation measures and by communicating the hazard clearly to the end users. The Applicant must justify the benefits of the products in relation to the risks, and the control of these risks.

2.2.1. Risk mitigation measures

Adverse effects on the environment from PBT substances should be prevented through the application of appropriate risk mitigation measures to ensure that any risks from the uses of a substance are adequately controlled, and with a view to progressively substituting these substances with a suitable safer substance, where feasible. For any substance fulfilling the P, B and T criteria, measures should always be taken to minimise, as far as technically and practically possible, emissions with a view to minimising the likelihood of adverse effects. Measures to ensure adequate control should be clearly described in the SPC and product literature when relevant, and in the conditions to the marketing authorisation, e.g. as Risk Management plans, periodic review or specific post-authorisation monitoring.

While it is recognised that for PBT substances it will be difficult to assess appropriate risk mitigation measures, as the emission quantification is difficult, effective risk mitigation measures should be explored that minimise release into the environment.

Targeted sampling / post-marketing monitoring in the environment following treatment in risk management plans could be envisaged to allow measurement of effectiveness of risk mitigation measures. However, experience with this is limited at present.

Each product must be evaluated according to its intended use, and all options for reduction of environmental release of the PBT substance must be used. This could be limitations in use of the product, for example:

- treatment only by injection, to avoid spillage or run-off
- treatment only while animals are in the stable, to avoid direct emission to the environment
- avoid the animals' access to water ponds or streams for a specified period after treatment, where excretion is high
- use only in small water tanks where waste water can be collected and safely managed, etc.

Such limitations should be based on robust justifications and data to ensure the effectiveness of the environmental protection.

2.3. Risk communication in SPC and labelling

For products containing PBT substances, information on bioaccumulation, persistence and degradability must be given in the SPC and leaflet, where available and appropriate. Information should also be provided for hazardous transformation products arising from the degradation of substances, if relevant. The information shall be consistent with the information provided in the dossier.

Where environmental risks have been identified, information on toxicity using data from tests performed on aquatic and/or terrestrial organisms must be provided, where relevant. This includes relevant available data on aquatic toxicity, both acute and chronic for fish, crustaceans, algae and other aquatic plants. In addition, toxicity data on soil micro- and macro-organisms and other environmentally relevant organisms, such as birds, bees and plants must be included, where relevant. This information must be reflected in the package leaflet so the end user can respect the risk mitigation measures adequately.

The octanol-water partition coefficient (Kow) and bioconcentration factor (BCF) of the substance should be included in the SPC, if available.

The SPC and leaflet text must be clear on the environmental risks, in particular specifying under which conditions the risk is a particular problem and what the consequences may be. The text must also explain if there are unknown scenarios, which may confer additional risks and therefore should be avoided, if relevant.

2.4. Benefit-Risk considerations

A PBT screening should not be understood as an automatic non-ability to authorise a VMP, as it constitutes a screening, particularly if based only on a minimum set of data.

For a product containing a PBT substance, an authorisation should only be granted if it is shown that the risks can be adequately controlled, or if the therapeutic benefits outweigh the risks to human and animal health and the environment arising from the use of the substance, and if there are no suitable alternative substances or technologies. This decision should only be taken after consideration of all of the following elements and taking into account all available knowledge:

(a) the hazard posed by the uses of the substance, including the appropriateness and effectiveness of the risk management measures proposed;

(b) the therapeutic benefits arising from its use and the implications of a refusal to authorise as demonstrated by the applicant or other interested parties;

(c) the analysis of the alternatives or any possibility to substitute the substance, as provided by the applicant or other interested parties;

(d) available information on the risks to human health or the environment of any alternative substances or technologies.

Furthermore, marketing authorisations could be subject to conditions, e.g. a Risk Management Plan (RMP) with time-limited review whose periods would be determined on a case-by-case basis, specific monitoring and specific pharmacovigilance requirements. The RMP could include targeted sampling and/or post-marketing monitoring in the environment following use/treatment to obtain a better understanding of the actual environmental exposure.

The final benefit-risk evaluation must take into account all available data from quality, safety and efficacy to ensure that the expected benefits outweigh the potential risks of the product.

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List of abbreviations

B criterion:	Bioaccumulative criterion
BCF:	Bioconcentration Factor
CLP:	Regulation on Classification, Labelling and Packaging
CVMP:	Committee for Medicinal Products for Veterinary Use
DT_{50T1}:	Degradation half-lives at temperatures T_1
DT_{50T2}:	Degradation half-lives at temperatures T_2
E_a:	Activation energy (kJ mol^{-1})
EC:	European Commission
$EC_{50;}$ $EC_{(X)}$:	The concentration of a test substance which results in 50% (X%) of the test animals being adversely affected, i.e., both mortality and sub-lethal effects
ECHA:	European Chemicals Agency
EFSA:	European Food Safety Authority
EIA:	Environmental impact assessment
EMA:	European Medicines Agency
EMEA:	Old acronym for European Medicines Agency (replaced by EMA)
ERA:	Environmental risk assessment
EU:	European Union
EU TGD:	European Union technical guidance document
FOCUS:	Forum for the co-ordination of pesticide fate models and their use
exp:	Exponential function
GL:	Guideline
K_{ow}:	Octanol-water partition coefficient
LC_{50}:	The concentration of a test substance which results in a 50% mortality of the test species.
NOEC:	No Observed Effect Concentration
OECD:	Organisation for Economic Co-operation and Development
P criterion:	Persistent criterion
PBT:	Persistent Bioaccumulative Toxic (chemical)
R:	Gas constant (0.008314 kJ K-1 mol-1)
REACH:	Registration, Evaluation, Authorisation and Restriction of Chemicals
STOT RE:	Specific Target Organ Toxicity after Repeated Exposure
T criterion:	Toxicity criterion

T_1:	Temperature 1
$T_{1/2}$:	Degradation half-life
T_2:	Temperature 2
VICH:	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP:	Veterinary medicinal product
vPvB:	Very persistent and very bioaccumulative